SEP 4 1931

VOLUME 23 NUMBER 3

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SEPTEMBER, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, July 10, 1925, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized July 29, 1920.

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ARCHIVES OF SURGERY

VOLUME 23 SEPTEMBER, 1931 NUMBER 3

HISTOLOGIC STUDIES OF THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

II. CHANGES IN THE CHOROID PLEXUS AND EPENDYMA *

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AND
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LOS ANGELES

As was outlined in a preliminary report by one of us,[1] a frequent observation in cases of fatal injury to the head is edema of the brain, as well as an increase in the amount of fluid in the ventricular system and in the subarachnoid spaces. We will discuss the question of changes in the brain substance in a later contribution. It is well known that in the majority of cases following injury to the head there is an actual increase in the amount of circulating cerebrospinal fluid. This may be demonstrated clinically by lumbar puncture, when it is usual to find an increase both in pressure and in the amount of recoverable fluid. Several questions present themselves: What is the source or sources of this fluid? Why should there be an excess of the fluid following trauma? What part, if any, does this increase of fluid play in the protective reaction of the brain? What is its bearing on the fatal issue in certain cases? What is its significance in the production of many of the late posttraumatic symptoms? Satisfactory answers to these and similar questions have never been given. It is evident that the increased amount of fluid is due to abnormal physiologic processes taking place within the brain. It is a common conception that the main source of cerebrospinal fluid is the choroid plexus. With this in mind we have been led to study the choroid plexus and ependyma histologically in fatal cases following head injury to see if any changes could be demonstrated which would indicate a hyperactivity of these structures.

Probably the first modern scientific explanation of the source of the cerebrospinal fluid dates from Haller[2] (1757) and Magendie[3] (1825), both of whom considered that it was a product of the leptomeninges, probably the pia mater. Faivre[4] (1853) first described the

* Submitted for publication, Dec. 5, 1930.

1. Rand, C. W.: Histologic Studies of the Brain in Cases of Fatal Head Injury: I. Preliminary Report, read before the Neurological Section of the American Medical Association, June 27, 1930.

2. Haller, A.: Elementa physiologiae corporis humani, Lausanne, M. Bousquet & Co., 1757.

3. Magendie, F.: Recherches sur le liquide cephalorachidien, Paris, 1825.

4. Faivre, E.: Des granulations meningiennes, Thèse de Paris, 1853, no. 142.

glandular structure of the choroid plexus and indicated that its epithelial cells were secretory. Luschka [5] (1855) described hyalin-like inclusions in the cells and also suggested that this structure was the source of the fluid. Findlay [6] (1899) made an exhaustive histologic study of the human choroid plexus under both normal and pathologic conditions. He believed that the epithelial covering of the choroid plexus and that of the ependyma were homologous, and he likewise described variation in the size of the individual epithelial cells. The granular nature of the cytoplasm of the cells, as well as the presence of hyaline droplets and vacuoles, was set forth in detail. He stated: "There is a constant change going on in the epithelial cells, and they normally undergo a process of vacuolation and rupture to form the choroid plexus secretion." Pettit and Girard [7] (1901, 1902), in a study of the choroid plexuses of animals, showed that the secretion was increased by the administration of muscarine, pilocarpine, ether and theobromine. Under such conditions they found that the height of the epithelial cells was practically doubled, and they described a granular basal and a clear apical zone of these cells which they interpreted as indicating increased secretory activity. Loeper [8] (1904) described pigmented granules and other granules within the vacuoles of the cells in the human plexus. Further histologic details of the epithelial cells in experimental animals, such as the presence of hyaline droplets and granules of fuchsinophilic or basophilic nature, were described by Schläpfer [9] (1905), Galeotti [10] (1897), Francini [11] (1907) and Engel [12]

5. Luschka, H.: Die Adergeflechte des menschlichen Gehirns, Berlin, G. Reimer, 1855.

6. Findlay, J. W.: The Choroid Plexuses of the Lateral Ventricles of the Brain: Their Histology, Normal and Pathological, Brain **22**:161, 1899.

7. Pettit, A., and Girard, J.: Processus sécrétoires dans les cellules de revêtement des plexus choroides des ventricules latéraux, consécutifs a l'administration de muscarine et d'éther, Compt. rend. Soc. de biol. **53**:825 (July 27) 1901; Sur la morphologie des plexus choroides du système nerveux central, ibid. **54**:698 (June 14) 1902; Action de quelques substances sur l'épithélium de revêtement des plexus choroides du système nerveux central, ibid. **54**:699 (June 14) 1902.

8. Loeper, M.: Sur quelques points d'histologie normale et pathologique des plexus chorioides de l'homme, Compt. rend. Soc. de biol. **56**:1010, 1904.

9. Schläpfer, V.: Ueber den Bau und die Funktion der Epithelzellen des Plexus chorioideus, in Beziehung zur Granulalehre und mit besonderer Berücksichtigung der vitalen Färbungsmethoden, Ziegler's Beitr. z. allg. Path. u. Anat. **7**:101, 1905.

10. Galeotti, G.: Studio morfologico e citologico della volta del diencefalo in alcuni vertebrata, Riv. di pat. nerv. **12**:480, 1897.

11. Francini, M.: Sulla struttura e la funzione dei plessi coroidei, Sperimentale, Arch. di biol. **51**:415, 1907.

12. Engel, E. A.: Ueber die Secretionsercheinungen in den Zellen der Plexus chorioidei des Menschen, Arch. f. Zellforsch. **2**:191, 1909.

(1909), who for the most part did not consider them secretory. On the contrary, Yoshimura [13] (1910) expressed the belief that the vacuoles were formed from an accumulation of the smaller granules as a step in the elaboration of cerebrospinal fluid, which is similar to Findlay's conception. Hworostuchin [14] (1911) described epithelial changes in the form of mitochondria which he believed to be associated with the process of secretion of cerebrospinal fluid. Pellizzi [15] (1911) believed that the granules were associated with the process of secretion but in a different manner. They were considered to absorb fluid plasm, gradually increasing in size until they were extruded from the free margin of the cell. Becht [16] (1920), in a critical review, doubted whether the choroid plexus acts as the major source of the fluid, leaving this an open question. Mestrezat [17] (1912) considered that the choroid plexuses form the cerebrospinal fluid by a process of dialysis. In addition to the foregoing histologic evidence, Weed [18] (1922) summed up in a very complete review the pharmacologic, pathologic and embryologic facts supporting the conception of the secretory activity of the plexus.

MATERIAL AND METHODS

Through the interest of Dr. A. F. Wagner of the coroner's department, abundant pathologic material was placed at our disposal. From this we selected sixty-one cases, most of which had been under our clinical observation. In addition, as a basis of comparison, we studied the choroid plexuses of ten persons who died of other conditions not involving the central nervous system. In all these cases, the body had previously been embalmed, so that the morphologic relationships of the plexus and the ventricle were preserved. The portion of the hemisphere containing the wall of the lateral ventricle and the enclosed plexus was delivered to us in a diluted solution of formaldehyde U. S. P. (1:10). Blocks were taken from the body of the lateral ventricle with its adjacent ependymal lining enclosing the glomus of the choroid plexus. Portions of the caudate nucleus, the thalamus and the overlying corpus callosum were included. These blocks were embedded in paraffin and stained by routine methods, hematoxylin and eosin stain being utilized as a standard for the study of the morphologic aspects of the plexus and the adjacent brain. Suitable sections were also studied with Herxheimer's method for fat, van Gieson's method for connective tissue and hyalin, and the Prussian blue method for iron. Normal and pathologic materials were treated in an identical manner.

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13. Yoshimura, K.: Das histochemische Verhalten des menschlichen Plexus chorioideus, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **18**:1, 1910.

14. Hworostuchin, W.: Zur Frage über den Bau des Plexus chorioideus, Arch. f. mikr. Anat. **77**:232, 1911.

15. Pellizzi, B.: Experimentelle histologische Untersuchungen über die Plexus chorioidei (Adergeflechte), Folia neuro-biol., Leipzig **5**:305, 1911.

16. Becht, F. C.: Studies on Cerebrospinal Fluid, Am. J. Physiol. **51**:1, 1920.

17. Mestrezat, W.: Le liquide céphalorachidien, Paris, A. Maloine, 1912.

18. Weed, L. H.: The Cerebrospinal Fluid, Physiol. Rev. **2**:171 (April) 1922.

CASE REPORTS

CASE 1.—*Diffuse subdural hemorrhage; death in four hours.*

A man, aged 55, was admitted to the Los Angeles General Hospital on Dec. 5, 1927, in an unconscious state, having been struck by an automobile a short time before. There was a large hematoma in the right side of the scalp. The right pupil was larger than the left. There was bleeding from the right ear and signs of a pathologic condition in the chest. He died about four hours after the injury.

The coroner's examination disclosed a laceration of the scalp in the right temporal region. There were abrasions and contusions of the face and both eyes were contused. A slight diffuse subdural hemorrhage was found, but no fracture of the skull. The first three ribs on the right side were broken, the lung was lacerated and the pleural cavity filled with blood. The cause of death was given as concussion of the brain with fracture of the ribs and laceration of the right lung.

Histologic Examination.—Choroid Plexus: There was an extensive diffuse edema of the stroma, showing localized collections of fluid. In some areas there was marked pigmentation of the stroma and choroidal epithelium (fig. 12). The pigment granules in the stroma were chiefly within large phagocytic cells, while those in the epithelium were largely in the vacuoles. In some areas of the stroma extensive extravasations of red blood cells and polymorphonuclear leukocytes were found. The blood vessels were empty and showed moderate distention. Numerous so-called "fibrin thrombi" were found within the vessels. Occasional psammoma bodies were present. The epithelial margins were irregular and torn in many places. The epithelial cells were marked by the presence of numerous vacuoles (64 per cent), some of which were extremely large (figs. 4 and 5). The basement membrane for the most part was intact. Masses of coagulated substance were found between the epithelial tufts. The average height of the epithelial cells was 20.39 microns.

Ependyma: There was practically no subependymal accumulation of fluid. Only a minor degree of ependymal vacuolization was present.

Comment.—This case showed the "full blown" type of choroidal changes, i. e., extensive edema of the stroma, increased pigment and red blood cells in the stroma, increased vacuolization (64 per cent) of the choroidal epithelium and an increase in the height of the choroidal cells (20.39 microns). Changes of this sort are often to be seen when death occurs from two to five hours after injury, There was a relatively small subependymal collection of fluid and only a minor degree of vacuolization of this membrane. This picture, which represents the most marked change in the plexus following an injury to the head, was found in five of our cases.

CASE 2.—*Extensive, depressed comminuted fracture of the right parietal and temporal bones; death in four days.*

A colored boy, aged 8, was admitted to the Los Angeles General Hospital at 4 p. m. on Dec. 10, 1927, in an unconscious condition, having been struck by an automobile. There was an extensive depressed fracture on the right side of the cranium. The right pupil was larger than the left; the left arm was rigid and deep reflexes on the left side were exaggerated. The spinal fluid was very bloody. spastic and occasional jacksonian twitchings on the left side were observed. The

Roentgenograms of the skull showed an extensive fracture of the skull, extending from 1 inch (2.5 cm.) above the external superior margin of the left orbit irregularly and transversely across the frontal bone into the right parietal region, associated with a stellate fracture in the right parietal region with depression. The patient never regained consciousness; he remained spastic on the left side and had occasional left-sided convulsive seizures. He died at 5:30 a. m. on December 14.

The coroner's observations were as follows: There were multiple contusions of the scalp and an extensive depressed fracture of the right parietal and squamosal bones. The fracture extended forward into the frontal bone, thence downward and toward the left across the floors of both anterior fossae of the skull. The cause of death was given as comminuted fracture of the vault and base of the skull.

Histologic Examination.—Choroid Plexus: There was practically no edema of the stroma; the blood vessels were small and empty. A small amount of pigment was found chiefly within the epithelial cells. The free epithelial margin was regular, showing only localized tendencies to distortion. The vacuoles were small and circumscribed and were present in 34 per cent of the cells; the average height was 15.98 microns.

Ependyma: There was practically no subependymal accumulation of fluid and only a minor degree of vacuolization.

Comment.—It is difficult to explain why there were so few changes in the choroid plexus or ependyma. The patient had all the signs and clinical symptoms of severe edema of the brain, yet at death the choroid plexus was little changed. It is possible that the choroid plexus passed through a stage of hyperemia which was subsiding at the time of death. It is also possible that the local injury was more prominent than general changes in pressure, which in comparison were of minor degree.

CASE 3.—*Basal fracture of the skull and subdural hemorrhage on the left side; death in ten hours.*

A Mexican, aged 37, was admitted to the Los Angeles General Hospital on July 5, 1929, in an unconscious condition, having been struck by a street car. A swelling on the left side of the head was noticed. The left pupil was dilated and fixed. The spinal fluid was very bloody. The patient was evidently in shock from which he never recovered. He died at 6 p. m. on the day of admittance to the hospital.

The coroner's examination showed multiple contusions of the head and face; a profuse subdural hemorrhage was found over the left side of the brain, associated with a fracture passing through the left middle and posterior fossae. The cause of death was given as fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—Choroid Plexus: There was a moderate degree of edema of the stroma, with accumulations of fluid here and there in the larger tufts (fig. 11). The blood vessels were tremendously dilated and a few small thrombi were observed. The epithelial margins were rather irregular, although not extensively torn. Numerous large vacuoles, some of which were seen breaking through the cells, were found throughout the epithelial covering. Sixty-seven per cent of the cells were vacuolated (fig. 3). There was a small amount of pigment in the vacuoles. Many of the nuclei also showed vacuolization and in some instances the nuclei were enclosed in vacuoles (fig. 8*B*). The average height of the cells was 20.34 microns. The basement membrane was torn in many places.

Ependyma: There was a moderate accumulation of fluid in the subependymal tissue. Localized areas of extensive vacuolization of the ependyma were observed, which in some places was almost detached from the underlying tissue.

Comment.—Marked change in the choroid plexus was present about ten hours after death; the blood vessels were tremendously dilated and there were marked edema of the stroma and vacuolization of the choroidal epithelium. The choroid cells were markedly increased in height (20.34 microns). The ependymal and subependymal changes were less marked than those of the choroid plexus.

CASE 4.—*Hemorrhage of the cerebrum and cerebellum; extensive body injuries; death within two hours.*

A woman, aged 70, was admitted to the Emergency Hospital at 7: 35 p. m. on Aug. 10, 1929, having been struck by an automobile. She was moribund on admission and there were evidences of extensive internal injuries to the chest and abdomen associated with fractures of the left leg and the right arm. She never regained consciousness, and died two hours following the injury.

On the coroner's examination the skull was not found to be fractured, but there was slight diffuse hemorrhage over various parts of the cerebrum and extensive hemorrhage covering the cerebellum. In addition to the intracranial condition, there were multiple contusions and abrasions of the body and extremities with fracture of the right humerus and the left tibia and fibula. There were many fractured ribs associated with a rupture of the diaphragm, liver and spleen with intraperitoneal hemorrhage. The cause of death was given as crushing injuries of the chest with concussion of the brain.

Histologic Examination.—Choroid Plexus: There was fairly extensive edema of the stroma with some tendency to accumulation of fluid in localized collections beneath the epithelium. "Fibrin thrombi" and concretions were numerous. The blood vessels were distended and empty. The epithelial margin was somewhat irregular. The vacuoles were variable in size, some being fairly large and well outlined, others small and found in the distal portions of the cells; 49 per cent of the cells were vacuolated. The average height of the choroidal epithelium was 17.25 microns.

Ependyma: There was practically no subependymal collection of fluid. There was moderate vacuolization of the ependymal cells, not more than is found in some normal brains.

Comment.—An increase in the percentage of vacuolization (49 per cent) and in the height of the choroidal epithelium (17.25 microns) together with fairly extensive edema of the stroma is a consistent observation two hours after a severe injury to the head.

CASE 5.—*Multiple basal fractures of the skull; fracture of the ribs, with laceration of the right lung; a fractured pelvis; death within one hour.*

A woman, aged 29, was admitted to the Emergency Hospital at 11: 49 p. m., on Aug. 11, 1929, having been injured shortly before when her automobile was struck by an electric train. She died at the time she entered the hospital. There was evidence of crushing injuries to the chest, skull and pelvis.

The coroner's examination showed numerous contusions and abrasions all over the body and head. The base of the skull was fractured in both the frontal and the right middle fossae. There was no definite injury or hemorrhage of the brain. There were many ribs fractured on both sides and in several places. The right lung was lacerated by several of these fractured ribs. The pelvis was fractured in two places, with laceration of the bladder by bone fragments. Both sacro-iliac articulations were torn loose, and there was extensive hemorrhage into all tissues of the surrounding pelvis. The cause of death was given as a fractured skull, a fractured pelvis and other injuries.

Histologic Examination.—Choroid Plexus: A minor degree of edema of the stroma was present, associated with only an occasional localized collection of fluid. The blood vessels were open and empty. The epithelial margins were fairly regular and the cells were only occasionally vacuolated (25 per cent), and in those the vacuoles were small and circumscribed. The average height of the cells was 12.33 microns.

Ependyma: In some situations, particularly about the blood vessels in the subependymal region, there were large collections of fluid. The ependyma was moderately but consistently vacuolated throughout its extent.

Comment.—The choroid plexus was practically normal, as the patient died before demonstrable changes in this structure could occur. It is likely that shock and hemorrhage played the principal rôle in bringing about the death of the patient, possibly altering the circulation in such a way as to prevent extensive vascular changes in the brain.

CASE 6.—*Mutiple fractures of the skull with laceration of the frontal lobes and an extensive subdural hemorrhage; death in four days.*

A woman, aged 30, was admitted to the Los Angeles General Hospital at 10:45 p. m. on Aug. 9, 1929, in an unconscious condition and shock. She was bleeding from both ears; a Babinski sign was present on the left side; the knee jerks were absent. There was marked rigidity of the abdomen. Intra-abdominal bleeding was suspected and a blood transfusion was given. She died without regaining consciousness.

The coroner's examination revealed multiple contusions, abrasions and lacerations of the head, body and extremities. An extensive subdural hemorrhage was found associated with lacerations of the lower half of the left lower frontal lobe of the brain and multiple fractures of the base of the skull. There were no internal injuries. The cause of death was given as fracture of the skull with laceration of the brain.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was present, although fairly large localized collections of fluid were found. The blood vessels were much distended and empty. Some free blood was observed in the ventricle, apparently outside of the epithelial tufts. In what was evidently the transverse cerebral fissure, from the appearance of adjacent structures, there were several collections of fibrin and leukocytes which suggested an infectious process, i. e., meningitis. The choroidal epithelium showed regular free margins. The cells were moderately vacuolized (31 per cent), the spaces being small and mostly confined to small ringlike clear zones about the nuclei. Finely granular pigment was situated almost entirely within the epithelial cells. Between the choroidal tufts were found small masses of what appeared to be fibrin in which

a few leukocytes were enmeshed. The average height of the cells was 13.84 microns.

Ependyma: There were some localized collections of fluid beneath the ependyma which was uniformly moderately vacuolated throughout its extent.

Comment.—This case showed evidences of inflammation in the choroid plexus, a condition sometimes seen after three or four days even in the absence of clinical or gross pathologic signs of meningitis. Edema of the stroma was only moderate in this case and little increase in vacuolization or height of the cells was found. The ependyma likewise showed little change. Laceration of the brain with subdural hemorrhage may have obscured the changes in the plexus or the changes may have become less prominent after the four day interval under the extensive administration of a hypertonic solution of dextrose.

CASE 7.—*Left occipital linear fracture; death in two days.*

A woman, aged 18, was admitted to the Los Angeles General Hospital at 12 noon on Aug. 14, 1929, in an unconscious condition, having fallen earlier in the day while hanging up clothes. There was bleeding from the left ear and a laceration of the scalp in the left occipital region. She died at 11:33 p. m. on August 16.

The coroner's examination showed an extensive subdural hemorrhage and extensive pulping of the right frontal lobe of the cerebrum. There was a fracture line in the left occipital and left temporal bone. The cause of death was given as fracture of the skull following a fall.

Histologic Examination.—Choroid Plexus: A moderate degree of edema was found in the stroma; in some areas it seemed absent altogether. The blood vessels were dilated and in many of them red blood cells were still present. An occasional intravascular "fibrin" thrombus was noted, but no concretions were found. The epithelial margins were ragged in many places and the distal portion of the cell seemed to be broken up. The vacuoles were not so numerous (36 per cent) as in some cases; they were moderate in size and did not contain pigment. The average height of the cells was 16.37 microns.

Ependyma: There seemed to be no subependymal accumulation of fluid except in a very few localized areas. The ependyma was not vacuolated beyond normal limits.

Comment.—In this instance there was practically no change in the stroma of the choroid plexus, although the vacuolization of the epithelium was considerably increased and the choroidal epithelium definitely elongated. One would expect more marked changes in view of the extensive cerebral damage found at autopsy, unless the energetic treatment with hypertonic dextrose solution had altered the existing conditions.

CASE 8.—*Multiple fractures of the skull and lower extremities; gas bacillus infection; death in thirty-six hours.*

A boy, aged 12, was struck by an automobile at 7 a. m. on Aug. 15, 1929. He was irrational on admission to the Los Angeles General Hospital. There was evidence of fracture of the skull and compound, comminuted fractures of the left

leg. He developed a *Bacillus welchii* infection in the lacerations of the left leg and died thirty-six hours after the injury.

The coroner's examination revealed a fracture of the floors of both anterior fossae of the skull, associated with a slight subdural hemorrhage diffused over the cerebrum. The lungs were emphysematous and there was a patch of hemorrhagic pleuritis between the lobes of the left lung. There was a deep laceration of the skin and soft tissues of the anterolateral surface of the left leg, which was swollen and discolored, associated with a compound fracture of both bones just above the ankle. A microscopic examination of the inflammatory exudate from the wound showed the presence of a gas bacillus. The cause of death was given as compound, comminuted fracture of the left leg with gas bacillus infection.

Histologic Examination.—Choroid Plexus: There was little distention of the stroma beyond normal limits. The blood vessels were empty and no localized collections of fluid of any magnitude were seen. The epithelial margins were fairly regular, the cells being quite uniform. Vacuoles were not numerous (33 per cent) and were small and circumscribed, many of them being little more than clear zones about the nucleus. In some cases vacuoles were seen between the cells. The basement membrane was intact in most places. The average height of the cells was 16.54 microns.

Ependyma: There was a fairly definite accumulation of fluid beneath the ependyma with fairly extensive vacuolization of its cells throughout.

Comment.—In this instance the ependymal changes both in vacuolization of the lining membrane and in evidence of subependymal tissue were greater than those of the choroid plexus. The latter showed only moderate vacuolization and some increase in the height of the choroidal epithelial cells. The apparent incongruity between the height of the cells and the percentage of vacuolization may be explained by the fact that, at least in our cases, the epithelial cells are normally higher in children than in adults. In this instance, as in cases 29 and 57, a gas bacillus infection caused death. It is possible that this patient might have recovered if the injury to the head had been the only factor involved.

CASE 9.—*Extensive subdural hemorrhage and contusion of the brain; death in two days.*

A man, aged 38, was admitted to the Los Angeles General Hospital at 11:30 p. m. on Aug. 11, 1929, in an unconscious state, with an odor of alcohol on his breath; he had been injured in an automobile accident. Aside from dilatation and fixation of the right pupil, there were no other positive neurologic signs. Roentgenograms of the skull showed a vertical linear fracture in the midoccipital region. He never regained consciousness and died at 3:05 p. m. on August 13.

The coroner's examination showed an extensive subdural hemorrhage associated with an extensive contusion of the lower surface of the right lower frontal lobe. There were fractures of the floor of the antrum and the posterior margin of the foramen magnum. The cause of death was given as fracture of the skull with contusion of the brain.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was present and was associated with some local accumulations of fluid. The epithelial margins were fairly regular, although in some individual cells small vacuoles

seemed to have broken through the margin, giving it a rather serrated appearance. The vacuoles were fairly small and circumscribed in most cases and some of them contained pigment granules. Some of the nuclei also contained vacuoles. Thirty-four per cent of the cells were vacuolated and their average height was 13.94 microns.

Ependyma: The subependymal accumulation of fluid was not above normal. Vacuolization of the ependyma was not increased.

Comment.—The degree of edema of the choroid plexus and ependyma was only moderate in this case and far less conspicuous than one would expect when injury to the brain and alcoholism were both present. The odor of alcohol may have been misleading in suspecting intoxication. Intensive intravenous treatments with a hypertonic solution of dextrose with an interval of two days may explain the lack of marked change in the plexus.

CASE 10.—*Extensive contusions of the brain with multiple fractures and internal injuries; death within twenty minutes after the fall.*

A man, aged 46, fell six floors down an elevator shaft at 8:10 a. m. on Sept. 23, 1929, sustaining crushing injuries of the head and chest with other body injuries. When the police ambulance arrived, about 8:30 a. m., the patient had died and the body was taken directly to the morgue.

The coroner's examination showed the skull to be extensively shattered and the brain contused and lacerated. All the ribs were found to be broken, each one in many places, with severe lacerations of the lungs. The liver and spleen were badly lacerated and ruptured and both kidneys were severely contused. There was a fracture of both clavicles, the left scapula, the right ileum and the lower end of the right humerus. The cause of death was given as crushing injuries of the head and chest with other injuries.

Histologic Examination.—Choroid Plexus: There was fairly extensive and diffuse edema of the stroma but no large accumulations of fluid were present. Pigment was present in the form of fine granules, found largely in the epithelial cells. The blood vessels were moderate in size, open and empty. The epithelial margins were fairly even although in some cells the distal margin was somewhat ragged. The vacuoles were moderate in size and fairly well circumscribed; they frequently contained rather coarse pigment granules. Twenty-six per cent of the cells were vacuolated; their average height was 13.9 microns.

Ependyma: There were no subependymal accumulations of fluid, although in many local areas there were rows of vacuoles which had collected beneath the nuclei, giving them a rather concentric appearance. Along the free margin of the ependyma in some areas, red blood cells could be found either intact or in the process of degeneration. Their presence was evidently due to ventricular hemorrhage (fig. 20).

Comment.—There was practically no increase in vacuolization or in the height of the cells, but fairly extensive edema of the stroma of the choroid plexus. Relatively greater vacuolization of the ependyma as compared with the choroid gives rise to the question whether ependymal changes occur sooner than choroidal changes after injury to the head. One also wonders whether fluid had collected in the stroma of the plexus

and had as yet failed to manifest its presence in the cells. The multiplicity of factors makes the time element a difficult one to evaluate satisfactorily.

CASE 11.—*Extensive subdural hemorrhage and basal fracture of the skull; death in twenty hours.*

A man, aged 24, was admitted to the Los Angeles General Hospital at 10:10 p. m. on Oct. 18, 1929, following an automobile accident. He was unconscious; the left pupil was dilated and fixed; the knee jerk was active on the right side, but absent on the left; a positive Babinski sign was found on the right. The spinal fluid was bloody and under greatly increased pressure. Both arms were spastic, the left more so than the right. He died at 6:15 p. m. on October 19.

The coroner's examination showed extensive subdural and extradural hemorrhage. There was an extensive fracture of the base of the skull, involving the middle fossae. No other injuries were found. The cause of death was given as fracture of the base of the skull with subdural and extradural hemorrhage.

Histologic Examination.—Choroid Plexus: There was a fairly extensive distention of the stroma, particularly in some portions of the plexus where there was much hemorrhagic extravasation. Fibrin and red blood cells were also found in the ventricular space. There were a few so-called "fibrin thrombi" and in one area were seen a group of concentric concretions. Open, not markedly distended blood vessels and small accumulations of fluid could be seen in the stroma. The free margin of the epithelium was smooth for the most part, although individual cells were somewhat ragged. The basement membrane was well preserved throughout, except where it bounded the larger fluid spaces. Vacuoles, while not numerous, were circumscribed and well defined; 25 per cent of the cells were vacuolated. Most of the free pigment was found in the epithelium. The average height of the choroidal epithelium was 15.56 microns.

Ependyma: There were no extensive subependymal accumulations of fluid. The ependyma was moderately and evenly vacuolated throughout its extent (fig. 18).

Comment.—The principal observation in this case was hemorrhage into the stroma of the choroid plexus and ventricular space. Numerous distortions and irregularities of the nuclei of the endothelial cells of the blood vessels were also shown. There was a minor increase in vacuolization and an increase in the height of the choroidal epithelium cells. The ependyma was moderately and evenly vacuolated throughout. Death was evidently brought about by local hemorrhage rather than by extensive edema of the brain.

CASE 12.—*Contusion of the brain and subdural hemorrhage; multiple fractures of the skull and internal injuries; death within an hour.*

A man, aged 28, was dead on admission to the Emergency Hospital at 11:59 p. m. on Oct. 19, 1929, having fallen from the second story of a building. He had apparently sustained multiple fractures of the skull and internal injuries.

The coroner's examination disclosed a severe general subdural hemorrhage associated with contusions of the base of the brain. There were multiple fractures of the skull involving the basal fossae, especially on the right side. The lungs were severely contused. The stomach was full of blood; no odor of alcohol was detected. There was some hemorrhage around the dorsal spine, but no fracture

was found. The cause of death was given as compound fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—Choroid Plexus: There was moderate edema of the stroma which seemed to involve the tufts somewhat irregularly, some being fully distended and others almost normal in appearance. Fluid spaces, often of considerable dimension, were seen here and there in the stroma. Blood vessels were open and occasionally contained red blood cells. In a few areas both within and without the villi small localized hemorrhages were found. Occasional small "fibrin thrombi," but no concretions, were seen. The free margin of the epithelium was quite regular, being broken up only in local areas. Free pigment, occasionally in good-sized masses and moderate in amount, was found within the epithelial cells. The basement membrane was well preserved everywhere. The vacuoles in the epithelium varied considerably in size, a few being larger than normal. Forty per cent of the cells were vacuolated. The average height of the epithelial cells was 16.31 microns.

Ependyma: There was no extensive subependymal accumulation of fluid. The ependyma was markedly vacuolated in some areas.

Comment.—The percentage of vacuolated cells (40 per cent) was rather more than one would expect when the patient survived his injury only a short time. The epithelial cells were also increased somewhat in size (16.31 microns). Edema of the stroma was also fairly extensive. It seems evident that there are numerous factors that influence the activity of the choroid plexus in injury to the head, so that it is difficult to evaluate the observations properly in some cases. In this case it is possible that the activity may have continued for some time post mortem.

CASE 13.—*Subdural hemorrhage with fracture of the skull; fractures of the left pubic bone and both bones of the left forearm; death in from two to three hours.*

A man, aged 61, was admitted to the Emergency Hospital at 6:41 p. m. on Oct. 19, 1929, in an unconscious condition, having been struck by an automobile shortly before. There was bleeding from the left ear and there were evident fractures of the left forearm and left leg. His condition became worse and he died at 8:45 p. m.

The coroner's examination revealed a fracture of both bones in the lower third of the left forearm. There were numerous severe contusions, abrasions and a long laceration of the outer aspect of the left leg. A severe general subdural hemorrhage was found. There was a large fracture of the skull, about 7 inches (17.8 cm.) long, extending along the base from the front to the rear on the left side, with some small side branches. The roof of the right orbit was splintered. No injuries of organs of the chest or abdomen were found. The left pubic bone was fractured and some hemorrhage had occurred into the surrounding tissues. The cause of death was given as fracture of the base of the skull with subdural hemorrhage and other injuries.

Histologic Examination.—Choroid Plexus: There was extensive edema of the stroma which seemed to be uniform throughout the plexus. Pigment was rather abundant and was confined almost entirely to the large vacuoles which were found in 66 per cent of the epithelial cells (fig. 9). The free margin of the epithelium

was irregular in many places. There was marked variation in the size of the individual cells, some of them being distended with a single large vacuole or several small ones. The basement membrane was frequently irregular, and in some places seemed to be indented by the underlying fluid (fig. 6). Almost all of the cell vacuoles contained irregular crystalline or granular pigment. The average height of the epithelial cells was 17.43 microns. Some cells were as high as 25 microns.

Ependyma: There was a moderate amount of subependymal edema. The ependyma was irregularly vacuolated; some areas had an abundant number while other parts were free from them.

Comment.—In this case there was marked edema of the stroma, with a great increase in vacuolization (66 per cent); the average height of the cells was also increased (17.43 microns). One cell measured 25.8 microns. Changes of this sort are to be expected, as the height of choroidal reaction apparently comes between two and four hours after injury.

CASE 14.—*Typical case of interval subdural hemorrhage; death four days later.*

A woman, aged 57, fell down four steps at 9 a. m. on Sept. 21, 1929, striking her head on the walk. She regained consciousness in a short time and remained clear until 3 p. m. on September 24. On that day the right pupil began to dilate and it remained dilated until her death. On the same day she went into coma with Cheyne-Stokes' respiration and a slow pulse rate. A diagnosis of subdural hemorrhage on the right side was made and she was brought about 75 miles to Los Angeles by ambulance on September 25. She died within an hour after arriving at the hospital.

The coroner's examination disclosed a large subdural hemorrhage in the right anterior, middle and posterior cranial fossae. The right pleural cavity contained about 1.5 liters of bloody fluid and the lower lobe of the right lung was severely contused and mushy. The cause of death was given as subdural hemorrhage.

Histologic Examination.—Choroid Plexus: There was a moderate degree of edema of the stroma which did not involve the plexus evenly. The blood vessels were distended and in some cases still contained red blood cells. Fluid spaces were to be found in some of the larger tufts. Fairly abundant pigment was found almost entirely in the epithelial cells. "Fibrin thrombi" were numerous and were scattered fairly evenly throughout the entire plexus. The epithelial margin was rather uneven, owing largely to the projection of swollen individual cells. Except in locations bordering the fluid spaces, the basement membrane was intact. The vacuoles in the cells were small and well outlined and usually hugged the nucleus; 64 per cent of the cells contained vacuoles. Pigment granules were scattered throughout the epithelial cells. The average height of the cells was 17.76 microns.

Ependyma: There was practically no subependymal accumulation of fluid, although in some places the cells were tremendously distorted and broken by vacuolization.

Comment.—Vacuolization was much increased (64 per cent); the height of the choroidal epithelium was increased (17.76 microns) and the stroma was moderately edematous, indicating increased activity of the plexus. These changes probably would have subsided if the patient

had been operated on opportunely and the subdural clot removed. We believe that such changes are not necessarily inconsistent with life.

CASE 15.—*Fracture of the base of the skull; subdural hemorrhage; death about three hours after injury.*

A woman, aged 62, fell down a flight of stairs on Oct. 19, 1929. She was taken to the Altadena Hospital where she died about three hours after admission.

The coroner's examination revealed a compound fracture of the base of the skull and severe general subdural hemorrhage, associated with severe lacerations of the brain. The cause of death was given as compound fracture of the base of the skull with laceration of the brain and subdural hemorrhage.

Histologic Examination.—Choroid Plexus: There was moderate edema of the terminal tufts of the plexus which seemed to involve them fairly evenly. Pigment was abundant and was confined almost entirely to the epithelial cells. "Fibrin thrombi" were common and several large concentric psammoma bodies were found. In the stroma fairly well circumscribed collections of fluid were found. In some places the fluid seemed to form clear, distinct, small open places in the stroma. The blood vessels were small and empty in most cases. There was marked variation in the height of the individual cells, some of them being very high. The vacuoles also varied considerably in size, some of them reaching such large proportions as practically to fill the cells, while others were small and circumscribed. In places vacuoles were seen within the nuclei (fig. 8*A*). Many contained pigment granules. Sixty-eight per cent of the cells were vacuolated; their average height was 19.83 microns.

Ependyma: There were minor subependymal accumulations of fluid and in some places the ependyma was much distorted and torn by the accumulation of vacuoles either within or just beneath the cells. In other places the ependyma seemed to be fairly intact and of normal proportions. The nuclei of the ependymal cells was frequently vacuolated. Discrete pigment granules were to be found in the ependymal cells.

Comment.—Again in this case there is a fairly typical picture of "full blown" choroidal changes, the patient dying three hours after injury. The choroidal vacuolization was much increased (68 per cent), the epithelial cells heightened (19.83 microns) and edema general throughout the stroma. The ependyma likewise showed moderate subependymal edema and marked vacuolization of ependymal cells in places.

CASE 16.—*Multiple fractures of the skull; subdural hemorrhage; fractured ribs; death within an hour.*

A man, aged 36, who had been struck by a truck, was dead when admitted to the Emergency Hospital at 4:53 p. m. on Aug. 23, 1929.

The coroner's examination disclosed multiple lacerations of the face and scalp; two fractures of the vault were found which ran parallel to the midline. Both extended into the frontal fossae on each side of the cribriform plate. There was also a marked subdural hemorrhage and a hemorrhage into the lateral ventricle. The fifth, sixth, seventh and eighth ribs on the left side were fractured in the nipple line. The cause of death was given as fracture of the skull with a subdural hemorrhage.

Histologic Examination.—Choroid Plexus: There was moderate edema of the stroma with a few localized collections of fluid. The tissue was marked by

hemorrhagic extravasations both within and without the tissues of the plexus. This probably accounted for the extensive pigmentation which marked the choroidal epithelium in almost every place. Few so-called "fibrin thrombi" were found. The blood vessels were distended and in many cases were filled with red blood cells. The epithelial cells were fairly regular in size and shape, being marked by an abundance of granular pigment in the cytoplasm. The free margins were somewhat irregular. The basement membrane was intact in most places. Vacuoles were not large and did not seem to be as abundant as in some cases of the series (43 per cent). The average height of the choroidal epithelium was 14.33 microns.

Ependyma: The ependymal tissue showed practically no evidence of accumulation of fluid, although in some places vacuolization of ependymal cells was extensive.

Comment.—Vacuolization of the choroid (43 per cent) was rather marked considering the fact that the patient died within an hour after his injury. The average height of the epithelium was not markedly increased. Edema of the stroma was moderate and ependymal changes were inconsequential.

CASE 17.—*Basal fracture of the skull with laceration of the brain and subdural hemorrhage; death in eleven days.*

A woman, aged 88, was admitted to the Los Angeles General Hospital at 11:14 p. m. on Oct. 10, 1929, in a confused condition, having fallen off the steps of her home shortly before. She was bleeding from the right ear and a contusion of the right parietal region was found. No deep reflexes were obtained. The spinal fluid was bloody and under pressure. Bronchopneumonia developed and the patient died at 6:10 p. m. on October 21.

The coroner's examination disclosed a fracture of the base of the skull with laceration of the brain and a subdural hemorrhage. The left temporal lobe of the brain was severely lacerated. The cause of death was given as fracture of the base of the skull with laceration of the brain and subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Extensive edema of the stroma was found which seemed to be rather diffuse for the most part, although some large fluid spaces were seen. There were numerous so-called "fibrin thrombi" and many large concentric calcospheres were observed in the larger portion of the stroma. The free margin of the epithelium showed considerable irregularity owing to marked enlargement of the individual cells some of which reached unusual proportions. Except in the regions of the large fluid spaces, the basement membrane seemed to be fairly well preserved. The vacuoles were large and discrete for the most part and frequently contained pigment. In some cells there were numerous small vacuoles which gave the epithelium a lacelike structure and gave an irregular outline to the cells. Sixty-two per cent of the cells were vacuolated. The average height of the choroidal epithelium was 17.16 microns. One free cell measured 26.3 by 17.6 microns.

Ependyma: There was a marked tendency to the accumulation of fluid in the subependymal space, but the ependyma itself showed little tendency to vacuolization.

Comment.—This case showed more extensive edema of the stroma of the choroid plexus than would have been expected after eleven days. Vacuolization was marked (62 per cent), and the average choroidal cell measured 17.16 microns. One free epithelial cell measured 26.3

by 17.6 microns, an enormous enlargement. There was also marked subependymal edema but practically no tendency to vacuolization of the ependymal lining. Could bronchopneumonia have been a factor in the swelling of this choroid plexus?

CASE 18.—*Compound, comminuted, depressed fracture of the skull; extensive subdural hemorrhage and laceration of the brain; death approximately nineteen hours after injury.*

A man, aged 26, was admitted to the Emergency Hospital at 6:07 p. m. on Oct. 6, 1929, in deep coma, having been struck by a freight train shortly before. There was clinical evidence of a fracture of the base of the skull and multiple lacerations were found on the forehead and face. He died at 2:10 p. m. on October 7.

The coroner's examination disclosed multiple lacerations of the face and scalp and a depressed comminuted fracture of the skull, 1 by 3 inches (2.5 by 7.5 cm.) in size, beginning in the anterior cerebral fossa on the left side and extending up into the left temporoparietal region. In addition, there were many fracture lines in the bones forming the base of the skull. There was extensive extradural and subdural hemorrhage and lacerations of the left frontal lobe of the brain. The cause of death was given as compound, comminuted, depressed fracture of the skull with laceration of brain.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was found which irregularly involved the terminal tufts of the plexus. Some of these seemed to be almost normal in their structure. The blood vessels were large and open and most of them were empty. There were a few small "fibrin thrombi" but no psammoma bodies. Finely granular pigment was present in a small quantity in the epithelium. A small amount of blood was found in the intervillous spaces. The epithelial margin appeared irregular in some places where the individual cells had become swollen and extended beyond their fellows. The vacuoles varied in size within wide limits, although they were not as numerous as in some cases. In many cases the vacuole was confined to a ringlike zone about the nucleus. Granular pigment was found in some of them. Fifty per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.57 microns.

Ependyma: There was little tendency to subependymal accumulations of fluid. In most places the ependyma was more vacuolated than normal; in other places it showed no vacuoles.

Comment.—There was less edema of the stroma than one would expect. Vacuolization of the choroidal epithelium was marked (50 per cent) and the cells were moderately heightened (15.57 microns). The ependyma showed an unusual amount of vacuolization with little subependymal edema. The comparatively low height of the average epithelial cell was due to the fact that while the cells were more frequently vacuolated, the vacuoles were very small. This would suggest a generalized but feeble reaction to injury.

CASE 19.—*Extensive subdural and ventricular hemorrhage and a lacerated brain; death in ten hours.*

A woman, aged 60, was admitted to the Los Angeles General Hospital at 8:30 p. m. on Oct. 17, 1929, in an unconscious state, having been hit by an auto-

mobile. The left pupil was dilated and fixed, and Cheyne-Stokes respiration was observed. The blood pressure varied from 210 systolic and 80 diastolic to 90 systolic and 40 diastolic. She died at 3:15 a. m. on October 18.

The coroner's examination showed a hemorrhage into the right upper eyelid, a few minor abrasions of the feet and a severe hemorrhage beneath the scalp. No fracture of the skull was found, but the entire lower half of the frontal and temporal lobes of the brain on the left side were lacerated to an extreme degree, being reduced to a pulpy mass. There was also marked extradural and intraventricular hemorrhage. The cause of death was given as severe laceration of the brain with subdural and intraventricular hemorrhage.

Histologic Examination.—Choroid Plexus: There was a moderate and symmetrical edema of the epithelial tufts. Abundant pigment was found both in the stroma and in the epithelium, explained probably by the hemorrhagic extravasations both within and without the choroid (figs. 13 and 14*B*). The blood vessels were moderate in size and most of them contained red blood cells. Numerous large "thrombi" and concentric psammoma bodies were scattered throughout the pedicle of the plexus. The epithelium was regular in outline and the cells showed little variability in their height and substance. The basement membrane was well preserved everywhere. The vacuoles of the cells were not large; they were usually discrete and in many cases were obscured by the abundant pigment. Thirty-eight per cent of the cells were vacuolated. The average height of the choroidal epithelium was 18.92 microns.

Ependyma: There was practically no tendency to accumulation of fluid beneath the ependyma which was unusually vacuolated. Some hematogenous pigment was found within the ependymal epithelium.

Comment.—The abundance of pigment was the most striking observation in the choroid plexus and this probably accounted for the small percentage of vacuolated cells, some of the vacuoles being obscured by masses of granular débris. There was considerable hemorrhage present in the stroma, which probably accounts for the presence of pigment.

CASE 20.—*Marked concussion and contusion of the brain with subdural hemorrhage; compound fracture of the right leg; fracture of the pubic bone; internal abdominal hemorrhage; death from three to four hours after injury.*

A woman, aged 60, was admitted to the Emergency Hospital at 5:33 p. m. on Oct. 18, 1929, with a history of having been struck by an automobile. She was unconscious on admission and never regained consciousness. There was a hematoma in the left parietal region. Other injuries were a laceration above the left upper eyelid, fractures of the upper third of the right tibia and fibula, and a compound fracture of the right pubic bone. She died at 9:05 p. m.

The coroner's examination revealed numerous minor contusions, abrasions and lacerations of the head and body. There were compound fractures of the bones in the upper third of the right leg. A large accumulation of blood was found beneath the entire scalp on the top and back of the head. No fracture of the skull or injury to the brain was found, but there was a severe general subdural hemorrhage. There was free blood in the abdomen and a fracture of the right pubic bone was found. The cause of death was given as injury to the head, a subdural hemorrhage and a fractured pelvis.

Histologic Examination.—Choroid Plexus: A moderate, evenly spread edema of the stroma was found which was marked in places by various-sized accumulations

of fluid. The blood vessels were much enlarged, open and almost entirely empty. Even the large pedicle of the plexus showed the marked effect of the edema; in some places it had the resemblance of a net. There were numerous well formed psammoma bodies as well as "fibrin thrombi." Practically no pigment was to be found. The epithelium showed considerable variation in the height of its cells as well as in the regularity of its free margin. The basement membrane was preserved over large fluid spaces, where it was drawn out into a row of flattened cells. The vacuoles varied considerably in size although none were very large; they were present in 34 per cent of the cells. The average height of the choroidal epithelium was 13.36 microns.

Ependyma: There was little accumulation of fluid in the subependymal spaces and only in one somewhat extended area was any degree of vacuolization shown. In this area the nuclei were distorted by the fluid droplets.

Comment.—The edema of the choroid pedicle was greater than that in other parts of stroma. Vacuolization of the choroidal epithelium was not as marked (34 per cent) as would be expected from the severe nature of the injury to the head. There was little increase in the height of the choroidal epithelium (13.36 microns). Ependymal changes were merely suggested. The picture was unquestionably modified by shock and intra-abdominal bleeding.

CASE 21.—*Large extradural clot and fracture of the base of the skull; death in two days.*

A man, aged 21, was admitted to the Los Angeles General Hospital at 12:30 p. m. on Oct. 6, 1929, having been hit on the head by a billiard cue about 9:30 p. m. the previous day. He was deeply comatose, and the left pupil was dilated and fixed. Roentgenograms of the skull showed a linear fracture of the left partietal bone. A left subtemporal decompression was performed at 1:35 a. m. on October 7, and an extradural clot was partially removed. He died at 8:15 p. m. on October 7.

The coroner's examination revealed a small laceration of the scalp in the region of the bregma. A large extradural clot was found which covered the lateral portion of the parietal lobe, measuring 4½ inches (11.4 cm.) in length, 3 inches (7.6 cm.) in width and about 1 inch (2.5 cm.) at its greatest depth. The base of the skull showed minute lines of fracture on the anterior surfaces of the middle portions of both petrosal bones, and there were hemorrhages in both orbits which could be seen through the orbital plates. A decompression operation had been performed and drains inserted. No internal injuries were found. The cause of death was given as basal fracture of the skull with extradural hemorrhage.

Histologic Examination.—Choroid Plexus: There was little edema of the stroma; this did not involve the entire plexus, some tufts retaining practically normal aspects. In those which were distended the blood vessels were wide and empty. A few so-called "fibrin thrombi" were seen, but no psammoma bodies were found. No hemorrhage or pigment in any quantity was observed. The epithelial margin was fairly regular in contour, the cells retaining their morphologic characteristic well. The basement membrane seemed to be well preserved in most places. The vacuoles were not abundant and were usually small and well circumscribed. Thirty-three per cent of the cells were vacuolated. The average height of the choroidal epithelium was 16.68 microns.

Ependyma: No subependymal edema and little vacuolization were found.

Comment.—Neither the choroid plexus nor the ependyma showed much alteration from normal. Vacuolization of the choroidal epithelium was moderately increased (33 per cent) and the choroidal epithelium was a little higher than normal (16.68 microns). The fluid spaces under the choroidal epithelium were rather large in places and pulsion vacuoles were seen pushing into the basement membrane of the choroidal epithelium. In this case it seems likely that local compression by the blood clot rather than general change was responsible for death. Such cases stand in marked contrast to those of severe injury to the head incident to traffic accidents.

CASE 22.—*Extensive subdural hemorrhage and laceration of the right temporal lobe; death in five days.*

A man, aged 35, was admitted to the Los Angeles General Hospital at 1:15 p. m. on Oct. 13, 1929, having been injured in an automobile collision. He was restless and semiconscious and was unable to swallow. The blood pressure was 95 systolic and 80 diastolic. On two examinations the spinal fluid was found to be very bloody and under great pressure. Roentgenograms demonstrated no fracture of the skull. He died at 3:30 p. m. on October 18.

The coroner's examination revealed a severe general subdural hemorrhage and an occipital extradural hemorrhage. Severe laceration of the lower portion of the right temporal lobe of the brain was also found. There was a fracture line from the right border of the foramen magnum outward, backward and inward for about 2 inches (5 cm.). The cause of death was given as fracture of the base of the skull with laceration of the brain and hemorrhage.

Histologic Examination.—Choroid Plexus: The connective tissue stroma was variably distended; in some places the edema was extensive, while in other places little change was noted. Some of the enlargement of the tufts was due to marked engorgement of the blood vessels and to hemorrhagic extravasation. There was also considerable free blood in the ventricular spaces. There were numerous and various-sized psammoma bodies in the pedicle of the plexus, and numerous so-called "fibrin thrombi" in the distal tufts. There was a moderate amount of pigment throughout the stroma (fig. 14*A*). The free margin of the epithelium was regular, although here and there individual cells projected. The basement membrane was intact almost everywhere. The vacuoles were not numerous (20 per cent) and for the most part were small and well circumscribed. The average height of the choroidal epithelium was 14.27 microns.

Ependyma: There were patches of vacuolization although most of the cells were normal. There was no subependymal edema.

Comment.—There was considerable but irregularly distributed edema of the stroma with hemorrhagic extravasation into the connective tissue and ventricular spaces. The choroidal epithelium and ependymal lining were practically normal. The patient lived for five days, but showed no evidence of inflammatory reaction in the choroid plexus as has been frequently seen in other instances.

CASE 23.—*Fracture of the skull; extensive subdural hemorrhage and laceration of the brain; death in four or five hours.*

A man, aged 65, was admitted to the Emergency Hospital at 4:25 p. m. on Sept. 8, 1929, with a history of having been struck by an automobile. He was in deep coma and did not regain consciousness. There were multiple abrasions and contusions about the body. The blood pressure was 62 systolic and 40 diastolic, and the pulse irregular; the patient died at 8:10 p. m. on the day of the injury.

The coroner's examination showed that the petrous portion of the right temporal bone was extensively comminuted, as was the floor of the right middle cerebral fossa. A large fracture line extended from this region upward and backward to the right occipital region, immediately beneath the scalp wound previously described. There was a severe universal subdural hemorrhage and extensive lacerations of the under surfaces of both temporal lobes of the brain. The fourth to the tenth ribs inclusive were found to be fractured in the posterior axillary line. The cause of death was given as compound, comminuted fracture of the skull with laceration of the brain.

Histologic Examination.—Choroid Plexus: A marked, but not symmetrically distributed, edema of the stroma was found. This tended to be diffuse, although in some tufts various-sized collections of free fluid could be made out. The blood vessels were markedly enlarged and in most places were filled with red blood cells. The free epithelial margin showed considerable variation in its regularity, retaining in some places its fairly smooth contour. In other places the distal ends of the epithelial cells were swollen, which gave them an irregular outline. Except in regions overlying the accumulations of free fluid, the basement membrane was intact. The vacuoles varied considerably in size, some being quite large while others appeared as small perinuclear globules or crescents. Twenty-two per cent of the cells were vacuolated. The average height of the choroidal cells was 13.7 microns.

Ependyma: There was a moderate and fairly extensive vacuolization with definite looseness of the subependymal tissue.

Comment.—A marked edema but practically no heightening of the choroidal cells was observed in this instance. One would expect greater change with death occurring from four to five hours after injury. The ependyma showed more extensive vacuolization and edema of the subependymal tissue than did the choroid. The low blood pressure probably indicated a degree of shock. In cases in which the patient is in shock during the short period of life, we have found only minor changes in the choroid.

CASE 24.—*Typical interval extradural hemorrhage on the left side; death approximately two days after injury.*

A boy, aged 14, was admitted to the Methodist Hospital on Sept. 3, 1929, having been knocked down by an automobile two days before and rendered unconscious for a short time. He was taken first to the Emergency Hospital, then to the General Hospital and then home. He was clear and conscious for three hours after being struck. At 2 p. m. on Sept. 2, he had a terrific headache on the left side of the head and within a few minutes he was delirious with pain. He soon became comatose and was taken to the hospital. Roentgenograms of the skull showed a fracture in the left temporoparietal region. About 8 p. m. on September 3 the left pupil became dilated, and general convulsions with extensor rigidities and double ankle clonus appeared. There was a rapid rise in temperature. The

breathing became irregular and the pulse rapid and weak. The patient died at 10:15 p. m.

The coroner's examination revealed a large extradural hemorrhage in the left temporal region. A fracture of the skull was found, the fracture line extending from the foramen ovale in the left middle cerebral fossa, across the floor of the fossa to the side of the skull on the left, thence upward and backward to a point just above and behind the left ear. The cause of death was given as fracture of the skull and extradural hemorrhage.

Histologic Examination.—Choroid Plexus: Moderate, but evenly distributed, edema of the stroma was found, marked by numerous and often by large fluid spaces. A small amount of pigment was found in the epithelium of the plexus. The epithelium was distended with various-sized vacuoles, which reached large proportions in some instances. Practically all of the epithelial cells showed a diffuse edematous change, which gave the cytoplasm a fine lacelike appearance. In many cases the nuclei were also vacuolated. Some of the nuclei also showed a horseshoe-shaped outline and rupture of the nuclear membrane (fig. 7*A* and *B*). Thirty-two per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 16.74 microns.

Ependyma.—There was a marked tendency to subependymal accumulations of fluid and in some localized places the ependyma was distorted and destroyed (fig. 19).

Comment.—This is the only case of extradural, interval hemorrhage in the series. The cells were edematous, but there was only a relatively slight increase of vacuolization and the choroidal epithelium was only moderately heightened. A marked subependymal edema was observed with great destruction of this membrane in places. Here again was a clearcut case of local, rather than general, pressure, and again the changes in the choroid were moderate. The patient would probably have lived had the hemorrhage been removed in time.

CASE 25.—*Fracture of the base of the skull with subdural and intraventricular hemorrhage; death in six hours.*

A boy, aged 4, was admitted to the Emergency Hospital at 6:15 p. m. on July 22, 1929, having been struck by an automobile a short time previously. He was unconscious and his condition was poor. He was discharged to the Los Angeles General Hospital, where he died about six hours after the injury.

The coroner's examination revealed a deep laceration of the left side of the upper lip and multiple contusions of the head and body. A fracture across the floor of the right middle fossa at the base of the skull was found, with a resultant subdural and ventricular hemorrhage and concussion of the brain. The right lung was also contused. The cause of death was given as fracture of the base of the skull, with concussion of the brain.

Histologic Examination.—Choroid Plexus: The stroma showed a moderate but symmetrically involved edema. Embedded in several large masses of fibrin, both within and without the stroma, were leukocytes and blood pigment. This suggested some degree of inflammatory reaction. There was a small amount of pigment diffusely spread throughout the epithelium. The basement membrane was distorted in many places by droplets of fluid either in the cell or just beneath it. The epithelial margin was extremely irregular, owing in most cases to a

marked distention of the distal portion of the individual cells. The vacuoles showed considerable variation in size and distribution. A few cells were almost completely occupied with large, clear spaces, while others were filled with numerous small irregular droplets. Fifty-four per cent of the cells were vacuolated. The average height of the choroidal epithelial cell was 19.35 microns. In many places the cells seemed to be separated by the accumulation of fluid beneath them.

Ependyma: An occasional localized accumulation of subependymal fluid was seen, especially about the blood vessels. The ependyma itself was free from vacuolization.

Comment.—Edema was moderate, but an inflammatory reaction was present throughout the stroma; this showed how early such a reaction could appear, as the patient died within six hours after injury. Vacuolization was marked (54 per cent) and the choroidal epithelium high (19.35 microns). The ependymal changes were slight in comparison with those of the choroid.

CASE 26.—*Compound, comminuted fracture of the skull; subdural hemorrhage and laceration of the brain; death in ten hours.*

A man, aged 38, was admitted to the Los Angeles General Hospital at 7:40 p. m. on July 19, 1929, in semicoma, having been struck by an automobile shortly before. He was in considerable shock. Roentgenograms of the skull showed a comminuted fracture involving the major portion of the left side of the cranium with a stellate fracture in the frontal region and a linear fracture into the parietal area. He died at 4:55 a. m. on July 22.

The coroner's examination showed ecchymosis around both eyes and over the left side of the head, and a laceration 1 inch (2.5 cm.) deep in the center of the forehead. A compound, comminuted fracture involving the left temporal region and the left middle fossa at the base of the skull was also found associated with laceration of brain tissue and subdural hemorrhage. The cause of death was given as fracture of the base of the skull with laceration of the brain.

Histologic Examination.—Choroid Plexus: Moderate generalized edema of the stroma was present, with a tendency to a circumscribed accumulation of fluid. The epithelial margin varied in regularity, but in no place did it present marked serration. The basement membrane seemed to be fairly well preserved throughout. The blood vessels were large, open and empty. The vacuoles varied to some extent in size, but some were unusually large. Forty-four per cent of the cells were vacuolated. The average height of the choroidal epithelial cell was 16.74 microns.

Ependyma: No change from the normal was observed.

Comment.—One would expect more changes in the choroid plexus in a patient dying in ten hours from the time of injury, particularly when the damage to the brain was so extensive. This is probably accounted for by the energetic treatment with hypertonic dextrose solution during the hours in the hospital.

CASE 27.—*Extensive comminuted fractures of the vault; laceration of the brain; intracranial hemorrhage; death in sixteen hours after injury.*

A man, aged 38, was struck on the left side of the head about 2 p. m. on Aug. 21, 1929, by a block of redwood 18 by 18 inches (45.7 cm.) and was

immediately rendered unconscious. There was bleeding from both ears. The left pupil was dilated and the patient had several generalized convulsions. Roentgenograms of the skull showed an extensive fracture, with ten different fracture lines in the vault and other fracture lines across the orbits and the bridge of the nose. The blood pressure was 140 systolic and 80 diastolic, the pulse rate 80 and respirations 20. He died at 6:10 a. m. on August 22.

The coroner's examination revealed large bruises of the right shoulder and the right side of the head with extensive hemorrhage into tissues behind the eyelids. There were extensive comminuted fractures of the vault and the base of the skull, with marked hemorrhage between the skull and the membranes covering the brain and between the membranes and the brain. There was also marked bruising of both frontal lobes of the brain. The cause of death was given as comminuted fractures of the vault and the base of skull, with contusions of the brain.

Histologic Examination.—Choroid Plexus: A marked generalized edema of the stroma was present together with some accumulations of fluid in the larger tufts. There was a large number of so-called "fibrin thrombi" scattered throughout the section. There was a small amount of pigment which was confined almost entirely to the epithelium. A few collections of red blood cells and of "fibrin masses" were to be found in the intervillous spaces. The epithelial margin varied considerably in regularity, some areas having a smooth contour, some being serrated and others appearing dentate. The basement membrane was distorted in many instances. The cells showed a moderate number of vacuoles, many of which contained granules of pigment. Forty-two per cent of the cells were vacuolated. These vacuoles varied considerably in size. The average height of the choroidal epithelial cells was 14.62 microns.

Ependyma: There was some looseness of the subependymal tissue suggestive of local edema. In some places the ependyma was moderately vacuolated.

Comment.—The degree of edema was the most marked factor in the choroidal changes. In this case the cells were moderately vacuolated (42 per cent) and little heightened (14.62 microns). The patient was twice given 50 cc. of 50 per cent dextrose solution intravenously. In spite of this, the choroid plexus showed marked changes and the gross changes in the brain were also extensive.

CASE 28.—*Moderate subdural hemorrhage; a crushed chest; internal abdominal injuries; death in about two hours.*

A man, aged 47, was admitted to the Emergency Hospital at 6:53 a. m. on Dec. 18, 1929, having been struck by an automobile shortly before. He was unconscious and remained so until his death at 7:53 a. m. The blood pressure was too low to be determined. There were evidences of multiple fractures of the ribs, internal injury of the chest and general bruising. Shock was pronounced.

The coroner's examination revealed multiple contusions, abrasions and lacerations of the head, body and extremities. No fracture of the skull was found, but there was moderate subdural hemorrhage at the base of the brain. No gross injury to the brain was found. All the ribs on the right side were found to be fractured in numerous places and the last six ribs on the left side were fractured in their posterior half. The sternum was completely fractured at the level of the third intercostal space. The right lung showed extensive subpleural lacerations. There was considerable retrosternal hemorrhage. There was a large

hematoma of the transverse mesocolon. Both kidneys showed considerable blood in the pelvis, but were otherwise in good condition. The cause of death was given as concussion of the brain and shock following injuries of the head and crushing injuries of the chest with multiple fractures of the ribs.

Histologic Examination.—Choroid Plexus: There was a moderate generalized edema of the stroma which involved the connective tissue of the pedicle as well as the distal tufts. In the larger spaces there were various-sized accumulations of fluid. There was a small amount of coarse granular pigment, which was confined largely to the stroma and the intervillous spaces. The epithelial margins showed considerable variation in their regularity. The basement membrane was distorted in many places owing to the local accumulation of fluid. The choroidal epithelium was marked by extensive vacuolization, the spaces varying considerably in size; some were so large as to fill the cytoplasm of the cell almost completely, while in other instances they were small and numerous and gave rise to a lacelike appearance. In the latter instance the free margin of the cell was irregular, probably incident to the rupture of these small vacuoles. A coalescence of two or more moderately sized vacuoles was not uncommon. Thirty-four per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 12.17 microns.

Ependyma: There were large localized collections of fluid beneath the ependyma, particularly about the subependymal blood vessels. In some places the ependyma was markedly vacuolated.

Comment.—Considerable generalized edema of the stroma was present in this case. The vacuolization, while not excessive (34 per cent), demonstrated well the presence of multiple vacuoles which were coalesced in a single cell. The average height of the choroidal epithelium was not increased (12.17 microns), probably because the vacuoles were small. There were unusually large localized accumulations of fluid beneath the epithelium. Had shock not been present, it is likely that this case would have shown a "full blown" type of choroidal change.

CASE 29.—*Compound, comminuted depressed fracture of the skull in the right frontal region; fracture of the right femur; gas bacillus infection of the right leg; death in six days.*

A man, aged 41, was admitted to the Santa Fe Hospital on Dec. 12, 1929. On December 10, while working in a gravel pit, he had been rendered unconscious for a few minutes by the explosion of a dynamite charge. He received a compound, comminuted, depressed fracture of the skull in the right frontal region, and a fracture of the right femur. There were lacerations of the lower extremities caused by flying pebbles and sand. When examined on December 13, he was clear and conscious, with no positive neurologic signs. On the night of December 13, he was somewhat irrational; his temperature rose to about 100 F. On the morning of December 14, he appeared clear. Under ether anesthesia, the depressed fracture in the right frontal region was elevated. At the same time a Steinman pin was put through the right femur by Dr. Chaffin, and skeletal traction was brought on the fracture. It was noted at the time that his right leg seemed larger than his left. On December 15, he complained of pain in his leg, but he was mentally clear. On the night of December 15, his temperature rose to 103 F., and the pain in his leg increased. On December 16, it was evident that a gas bacil-

lus infection of the right leg had occurred. Amputation of the right leg was carried out, and a blood transfusion was given. The patient died about 2 p. m.

The coroner's examination revealed what appeared to be a laceration, 3 inches long, in the right frontoparietal region. This had been sutured and there was a gutta-percha drain in place in the upper angle of the wound. The right thigh had been amputated at about the junction of the middle and upper thirds. The appearance of the stump indicated that an emergency amputation of a badly mangled and probably infected leg had been performed. An elliptical, comminuted, depressed fracture of the skull, 1¼ inches by 1¾ inches (3.1 by 4.4 cm.), was found in the right frontal region immediately under the laceration previously described. No injury to the brain was found but there was a moderate amount of subdural hemorrhage. The second and third ribs on each side were found to be fractured in the midaxillary line. The cause of death was given as shock and hemorrhage following mangling injuries of the right leg and other injuries.

Histologic Examination.—Choroid Plexus: Moderate generalized diffuse edema of the stroma was present. The blood vessels were moderate in size and empty in practically every case. The epithelial margins were somewhat irregular; the basement membrane was intact in most places and was not markedly distorted. The vacuoles of the epithelium varied considerably in size, some being very small and others assuming large proportions. Some cells contained several large vacuoles which almost entirely replaced the cytoplasm. Thirty-six per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 16.14 microns.

Ependyma: Practically no vacuolization or subependymal edema was found.

Comment.—In this instance there was moderate diffuse edema of the stroma as well as increased vacuolization (36 per cent) of the choroidal epithelium. The cells were somewhat heightened (16.14 microns). No vacuolization of the ependyma and no subependymal edema were found. This patient would almost certainly have recovered from the injury to the head alone, as it consisted of a moderately depressed frontal fracture which was elevated. In addition, he had concussion of the brain. His death was due to a gas bacillus infection of the right leg. It is felt that the changes found in the choroid plexus described often occur in various types of injury to the head from which the patient recovers.

CASE 30.—*Moderate subdural hemorrhage; multiple fractures of the ribs, right forearm and left ankle; death in six hours.*

A man, aged 62, was admitted to the Emergency Hospital at 6:40 p. m. on Dec. 16, 1929, having been struck by an electric train at about 6 p. m. He was transferred to another hospital where he died at about 10 p. m. No adequate record of a physical examination was found.

The coroner's examination revealed multiple abrasions and contusions of the head, body and extremities. The right ulna, the first two ribs and last six ribs on the right side and the sixth rib on the left side were fractured. There was also a dislocation of the ninth on the tenth dorsal vertebra, and of the left sacroiliac articulations. There was slight subdural hemorrhage, but the brain showed no gross evidence of old or recent injury. Severe contusions and hemorrhages into the muscles of the front and right side of the chest were found. The right

lung was severely lacerated and collapsed and the right pleural cavity was filled with blood. There was a dislocation of the ninth on the tenth thoracic vertebra, with free motion between these two vertebrae. The muscular layers of the stomach wall were ruptured for almost the entire length of the anterior wall of the stomach, but the mucosa and peritoneum were still intact. The liver showed some contusions, but no actual rupture was found. There was complete separation of the left sacro-iliac articulation. The cause of death was given as hemorrhage from multiple fractures of the ribs and a lacerated lung, with other severe injuries.

Histologic Examination.—Choroid Plexus: There was extensive edema of the stroma which involved the whole plexus. Numerous large collections of fluid were found. The blood vessels were open but not particularly distended and in a few cases they contained red blood cells. Numerous "fibrin thrombi" and calcospheres were found, the latter being most abundant in the pedicle of the plexus. Coarse granular pigment was found in moderate amounts both within the stroma and in the intervillous spaces. In the stroma were found large phagocytic cells loaded with light brown pigment. The epithelium showed considerable variation in the contour of its free margin. The basement membrane in most places had been either compressed or distorted by the underlying accumulation of fluid. The vacuoles showed considerable variation in size and distribution; some of them were very large but most of them were moderate in size. In a few individual cells the cytoplasm was tremendously swollen; on close inspection it was found to be loaded with minute vacuoles. Under higher magnifications, the connective tissue of the stroma was seen to be separated by the fluid to form a fine meshwork of fibrils. Thirty-five per cent of the cells were vacuolated and the average height of the choroid epithelium was 13.76 microns.

Ependyma: The ependymal lining was symmetrically and moderately vacuolated. There was no subependymal edema.

Comment.—This was an example of extensive edema of the stroma of the choroid plexus. There was also a considerable increase in pigmentation. Vacuolization was not greatly increased (35 per cent) and the choroid epithelium was of about normal height (13.76 microns). The choroid picture should probably be classified as of the "full blown" type. A maximal amount of edema was present, death occurring approximately six hours after injury. The ependyma and subependymal tissue showed relatively little change.

CASE 31.—*Extensive subdural hemorrhage; period of survival after injury not known.*

A man, aged 57, was admitted to the Los Angeles General Hospital, unconscious and in deep shock, having been picked up by an ambulance at the base of the San Gabriel Canyon. No physical examination was made as the patient died five minutes after arrival at the hospital.

In the coroner's examination no fracture of the skull was found. There was an extensive subdural hemorrhage as well as some hemorrhage into the base of the brain. The cause of death was given as subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Extensive and diffuse edema of the stroma was found involving both the pedicle and the distal tufts. There was a tendency toward localized collections of fluid in the stroma. In one area, apparently in the stroma of the pedicle, was found a tremendous number of

macrophages loaded with débris. In the better stained portions of this area the débris had a reddish cast which seemed to be of the nature of blood pigment. There were fairly numerous "fibrin thrombi" in the peripheral tufts, and numbers of well formed concentric psammoma bodies were found throughout the pedicle. The blood vessels were open and many of those in the distal tufts contained red blood cells. The free margin of the choroidal epithelium was regular in contour in most places. The cells were not extensively vacuolated. Those that were present varied in size from small concentric, clear zones about the nucleus, to large, well circumscribed vacuoles filling the major portion of the cell. The basement membrane was somewhat distorted by the edema of the stroma and may have been destroyed in the regions bounding the larger fluid space. Twenty-six per cent of the cells were vacuolated. The average height of the choroidal epithelium was 11.03 microns. There was a little coarse granular pigment, chiefly in the ventricular space.

Ependyma: There were no alterations except for minor vacuolization in some places, which was not beyond the limits of normal. No subependymal edema was present.

Comment.—The exact nature of the injury or the time that elapsed between the injury and death are not known. The changes in the stroma of the choroid plexus, however, were marked. There was extensive edema with many macrophages loaded with débris. This last observation probably indicates destruction of blood and phagocytosis rather than inflammatory changes in the choroid plexus. The observation that the "full blown" type of choroid plexus appears between two and four hours after injury may indicate that this patient died about that long after his injury.

CASE 32.—*Basal fracture of the skull with subdural hemorrhage; death within an hour.*

A woman, aged 64, was injured about 8:30 p. m. on Jan. 23, 1930, when she was struck by a hit and run driver. She was dead when picked up by the police. The body was taken directly to the coroner.

The coroner's examination revealed multiple extensive contusions about the head, body and extremities and a compound fracture of the bones of the left leg. There were severe comminuted fractures of almost the entire base of the skull, with severe general subdural hemorrhage. Both lungs showed moderate contusions. The cause of death was given as comminuted fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Moderate edema of the connective tissue stroma was present which seemed to involve the plexus asymmetrically. The pedicle seemed to be more involved than the distal tufts, some of which retained almost their normal morphologic appearance. The blood vessels were open and many of them still contained red blood cells. "Fibrin thrombi" were fairly numerous and an occasional small psammoma body was found. The epithelium showed a fairly regular contour, although here and there marked variations in individual cells were noted. The vacuoles varied considerably in size. In some cells they were numerous and small, giving a lacelike appearance to the cytoplasm, while in others they were large and well outlined. Thirty-nine per cent of the cells were vacuolated. The average height of the choroidal epithelium

was 13.98 microns. In many places the basement membrane had been compressed and distorted. No pigment was to be found in the epithelium or stroma.

Ependyma: The ependyma seemed to be free from vacuolization. The subependymal tissue seemed to be somewhat loose and edematous. Along the ventricular margin red blood cells were seen clinging to the outer surface of the epithelium.

Comment.—In this instance death was due primarily to the injury to the patient's head, and it occurred within an hour, possibly within a few minutes, of the time of the accident. Fulminating subdural hemorrhage, multiple fractures of the skull and moderate edema of the stroma were present. For the most part, the vacuoles were small, breaking the cytoplasm of the cells into lacelike strands. Possibly death occurred before extensive large vacuole formation had time to develop.

CASE 33.—*Basal fracture of the skull; general subdural hemorrhage; fracture of both bones of the left leg; fractured ribs and a torn lung; death in two hours.*

A Japanese girl, aged 4 years, was struck by an automobile, at about 3 p. m. on Jan. 13, 1930. She was taken to the Emergency Hospital and was then transferred to the Japanese Hospital. She was badly shocked, having signs of fractured ribs and clavicle and of hemothorax. The left tibia and fibula were broken. She died at 5:30 p. m.

The coroner's examination showed multiple contusions and lacerations of the body and extremities and a compound fracture of both bones of the left leg. A moderately severe general subdural hemorrhage was found, together with a basal skull fracture, 1¼ inches long, extending backward from a point near the inner end of the petrous portion of the right temporal bone. The right lung was collapsed and the right pleural cavity contained about a pint of blood. The upper lobe of the right lung was torn almost completely in two. There was a fracture of the first right rib near its sternal end. The cause of death was given as hemothorax from a ruptured lung and other severe injuries.

Histologic Examination.—Choroid Plexus: There was moderate edema of the stroma which involved the terminal tufts symmetrically. The edema seemed to be rather diffuse, although some tendency to local collections of fluid could be observed. The blood vessels were open and empty. There were a few "fibrin thrombi" scattered throughout the section, but no psammoma bodies could be seen. The epithelial margin showed considerable variation in regularity, some places being smooth, while others were much distorted and torn. There was likewise an extensive variation in the vacuoles, some of which were large. Twenty-eight per cent of the cells were vacuolated. In many places the cellular edema was manifested by a collection of small droplets, especially near the distal portion of the cell. The rupture of these small droplets into the ventricular space was probably the explanation for the torn appearance of the epithelial margin. The average height of the choroidal epithelium was 12.10 microns. The basement membrane seemed to be considerably distorted and compressed by the fluid in the stroma.

Ependyma: In some places there seemed to be a definite tendency to subependymal collections of fluid and the ependyma was moderately vacuolated; otherwise it showed no change from the normal.

Comment.—In this instance there was fairly marked edema of the stroma, as well as general edema of the choroidal epithelium. Vacuolization took the form of small droplets. Death occurring within two hours may explain why larger vacuoles were not formed and why more cells were not vacuolated. There was also considerable subependymal edema.

CASE 34.—***Basal fracture of the skull; subdural hemorrhage; both legs broken below the knees; death in from four to five hours.***

A man, aged 34, was struck by an automobile on the evening of Jan. 13, 1930. He was taken to the Emergency Hospital, where he died at 11:45 p. m. There were fractures of both legs below the knees and general bruising.

The coroner's examination revealed multiple contusions and lacerations of the face and scalp. Both bones of both legs were broken just below the knees. A severe general subdural hemorrhage was found. There was a fracture of the base of the skull, consisting of two fracture lines, each about 1 inch long, in the floor of the left anterior cerebral fossa. The cause of death was given as fracture of the base of the skull, with subdural hemorrhage and shock following other severe injuries.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was found which involved the plexus symmetrically. Many of the tufts were torn and distorted, suggesting a loss of solidarity of the connective tissue stroma. The blood vessels of the terminal tufts were moderate in size and still contained red blood cells in many instances. There were occasional "fibrin thrombi" but no concretions were found. The free margin of the epithelium showed consistently an irregular outline, owing largely to swelling of the distal portions of the epithelial cells. The large vacuoles were not as common as in some of the other cases of the series, but the cells seemed to be marked by diffuse edema which filled the cytoplasm in the form of numerous tiny droplets. Twenty-seven per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 12.04 microns. The basement membrane was almost universally compressed, distorted or torn by the underlying collections of fluid or edematous stroma.

Ependyma: The subependymal tissue was loosely arranged as though filled with fluid, and the overlying epithelial cells were extensively vacuolized with marked distortion of their nuclei.

Comment.—In this instance edema of the choroid plexus stroma and subependymal spaces was moderate. Vacuolization of the choroid epithelium consisted of tiny droplets filling the cytoplasm. Vacuolization of the ependyma was marked, causing great distortion of the nuclei. Shock probably was a large factor in bringing about the patient's death and in all likelihood is the explanation for the absence of more marked changes in the plexus.

CASE 35.—***Basal fracture of the skull and fulminating subdural hemorrhage; death within an hour.***

A boy, aged 9, was struck by an automobile while crossing the street. He immediately became unconscious, and was dead by the time the ambulance reached the Emergency Hospital. No physical examination was recorded.

The coroner's examination revealed a moderate contusion of the right shin, a contused abrasion on the inner side of the left foot and a compound fracture of both bones of the left leg at about the junction of the middle and lower thirds. A severe general subdural hemorrhage was found. There were severe multiple fractures of the base of the skull. Fractures through the foramen magnum, of the first cervical vertebra and of the odontoid process of the second cervical vertebra were seen with partial dislocation of the skull on the atlas. The cause of death was given as fracture of the base of the skull with subdural hemorrhage and fractures of the cervical vertebrae.

Histologic Examination.—Choroid Plexus: Fairly marked and symmetrically disposed edema of the connective tissue stroma was observed. This seemed to be rather diffuse, with a minor tendency to localized collections of fluid. Some coagulated fibrin and red blood cells undergoing decomposition were found in the ventricular space. The blood vessels were open and in some instances contained red blood cells. Under low magnification the epithelial margin in the main appeared regular, but when observed under higher power it showed considerable laceration. The vacuoles were not as abundant as in some cases, and large ones that filled the entire cell were the exception. The cytoplasm manifested its fluid content by the presence of numerous small droplets, which gave the cell a coarsely granular appearance. Thirty per cent of the cells were vacuolated. The average height of the choroidal epithelium was 13.86 microns. The basement membrane was frequently irregular and compressed by droplets of fluid in the stroma (fig. 10). In a few circumscribed areas large phagocytic cells containing brown pigment could be found.

Ependyma: There was little tendency toward subependymal collections of fluid, although the epithelium in some areas was markedly vacuolated. In most places it showed no change from the normal.

Comment.—When one considers that the patient was dead within an hour of the time of the injury, one is surprised at the amount of edema found in the stroma of the choroid plexus. Vacuolization of the choroid epithelium had also begun to increase (30 per cent). There was little change in the ependymal or subependymal tissue.

CASE 36.—*Depressed fracture of the skull, subdural hemorrhage and secondary meningitis; death in four days.*

A Japanese, aged 52, was struck by a street car at 10:30 p. m. on Jan. 20, 1930. He sustained a fractured skull together with severe bruises. Meningitis subsequently developed, and he died at 10:05 p. m. on January 24.

The coroner's examination revealed multiple lacerations and contusions of the head, body and extremities. A severely comminuted, depressed fracture was found in the left anterior and middle cerebral fossae, extending up onto the left parietal bone. There were severe contusions of the lower surfaces of the brain, severe general subdural hemorrhage and hemorrhage into the pons; on the surface of the right cerebral hemisphere there was a large area covered by a fibrinopurulent exudate. The cause of death was given as a compound, comminuted, depressed fracture of the base of the skull with contusions of the brain, subdural hemorrhage and secondary meningitis.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma involved the plexus asymmetrically. Many of the distal tufts and localized areas of the pedicle, particularly about the larger vessels, were markedly distended.

Others retained a more nearly normal morphologic appearance. There seemed to be some localized masses of pigment in the region of the larger blood vessels, but this was not the rule. The blood vessels were open and for the most part empty. "Fibrin thrombi" were numerous in the distal tufts and an occasional psammoma body was found in the pedicle. The epithelium showed a marked irregularity of its free margin owing to swelling of the individual cells. The vacuoles were fairly numerous and in many cells reached unusual proportions. Forty-seven per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.56 microns. Some of the individual cells were more swollen by a diffuse edema than by circumscribed vacuoles. The basement membrane was indistinct, in some places owing to a diffuse swelling of the subepithelial connective tissue.

Ependyma: There was little tendency to subependymal accumulation of fluid. Throughout the extent of the ependyma the lining cells were practically free from vacuoles.

Comment.—In spite of the fact that the patient died of secondary meningitis, as shown by the coroner's report, study of the choroid plexus revealed no evidence of recent inflammation. Several other instances (cases 6, 40 and 41) showed undoubted signs of infection in the choroid plexus, but grossly no evidence of meningitis was made out. In this instance, vacuolization (47 per cent) was fairly marked, and the choroidal epithelial cells were considerably heightened (15.56 microns). The ependyma and subependymal tissues showed little change.

CASE 37.—*Concussion; compound fracture of the base of the skull; subdural hemorrhage.*

A man, aged 65, was found lying dead in a storm drain in one of the city parks. There was a wound on the head. It was thought that he stumbled into the drain the previous night.

The coroner's examination revealed several large lacerations and contusions about the head and extremities. A slight degree of subdural hemorrhage was found associated with multiple fractures of the base of the skull. The vessels of the brain were sclerotic, and one small vessel at the base on the right side was completely closed by the sclerotic process. A small necrotic area in the posterior portion of the right internal capsule of the brain was evidently of several weeks' standing. The cause of death was given as concussion of the brain and subdural hemorrhage following compound fracture of the base of the skull; contributory factors were cerebral arteriosclerosis and degeneration.

Histologic Examination.—Choroid Plexus: A moderate degree of edema was present which did not involve the plexus symmetrically. Some tufts showed little change from normal. There were a few so-called "fibrin thrombi" in the terminal tufts and an occasional psammoma body in the pedicle. There were red blood cells in the ventricular space. The epithelial margin was irregular, owing chiefly to swelling of the distal end of individual cells which gave a sort of dentate appearance to the outline of the villus. The cells seemed to be much elongated and many of them contained large vacuoles. In some the vacuoles were small and maintained a position close to the nucleus. Thirty-nine per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.48 microns. The basement membrane was not always clearly made out because of the collection of fluid in the stroma beneath it. The blood vessels were open and many of them contained red blood cells. No pigment was found in the epithelium.

Ependyma: There was a definite tendency to the subependymal accumulation of fluid and in most places the epithelium was more vacuolated than normal.

Comment.—In this instance the method of injury was obscure. It was also unknown how long after injury the patient died, or how long he had been dead when found. The study of the choroid plexus and ependyma would indicate that this had been some time, probably more than six hours, as there was considerable edema of the stroma.

CASE 38.—*Compound fracture of the base of the skull; a lacerated brain; subdural hemorrhage; death in four hours.*

A man, aged 64, was struck by an automobile while waiting for a street car. He arrived at the Emergency Hospital at 5:01 p. m. on Jan. 23, 1930, and died at 9 p. m.

The coroner's examination revealed multiple lacerations and contusions of the head and extremities. A fracture of the base of the skull with very severe generalized subdural hemorrhage was found. There was also severe laceration of the lower portions of both frontal lobes of the brain and the left half of the cerebellum was almost completely destroyed. The base of the skull was extensively fractured. The third, fourth and fifth left ribs were found to be fractured in the posterior axillary line. The cause of death was given as compound fracture of the base of the skull with lacerations of the brain and subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Extensive edema was observed which involved the choroid plexus quite evenly. In many places various-sized fluid spaces were found. Numerous so-called "fibrin thrombi" were found scattered throughout the plexus. The blood vessels were open and in most cases empty; considerable hemorrhage was found in the ventricular space. The free margin of the epithelium appeared irregular in many places, apparently owing to the rupture of many small, distally placed vacuoles. The vacuoles appeared to be of one or two sizes, the first appearing as fairly small, definitely circumscribed spaces, and the others as larger spaces which in some instances filled the cytoplasm. Fifty-one per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.56 microns. A diffuse cellular edema was manifested by numerous clear droplets which filled the cytoplasm of some of the cells. Pigment in finely divided granules was found in some of them. The basement membrane was irregular and torn in many places owing to local accumulations of fluid.

Ependyma: The subependymal tissue in most places was solid except where the ependyma became continuous with the epithelium of the plexus. Here the tissue appeared much looser and the tall ependymal cells were much vacuolated. In one or two other places the ependyma was vacuolated to a slight degree.

Comment.—The patient died approximately four hours after being injured. The choroid plexus showed marked changes. Edema of the stroma was extensive, vacuolization of choroidal epithelium marked (51 per cent) and individual cells considerably heightened (15.56 microns). The choroidal epithelium also appeared edematous. The choroid plexus resembled the "full blown" type which has been consistently seen in cases in which death occurred from two to four hours after injury.

CASE 39.—*Subdural hemorrhage and pneumonia; death in five days.*

A Mexican, aged 60, was brought to the California Lutheran Hospital at 12:40 p. m. on Jan. 20, 1930, in an unconscious condition. He could be aroused enough to talk, but was unable to give any details regarding his injury. He soon became irrational and delirious and died at 1:30 a. m. on January 25.

The coroner's examination showed multiple abrasions, contusions and lacerations about the head, body and extremities. No fracture of the skull was found, but there was a severe general subdural hemorrhage. Both lungs showed extensive consolidation and contusions. The first six ribs on the left side were fractured near their sternal ends and the first three ribs on both sides showed fractures near their vertebral ends with jagged ends protruding into the cavity of the chest. The cause of death was given as subdural hemorrhage following injury to the head, pneumonia following fracture of the ribs and contusions of the lungs.

Histologic Examination.—Choroid Plexus: The edema of the plexus stroma was asymmetrical. Some villi, particularly those along the main pedicle, were tremendously swollen, while other more distally placed tufts showed a minor degree of change. The blood vessels were wide and mostly empty. In the base of the pedicle of the plexus there was an extensive hemorrhagic extravasation. A few "fibrin masses" were scattered throughout the field. The epithelial margin was regular, as was the basement membrane in most places. Over various local accumulations of fluid the latter was either torn or compressed. The epithelium showed a moderate degree of vacuolization, the clear spaces being in the form of either intermediate-sized vesicles or tiny droplets. Thirty-five per cent of the cells were vacuolated. In the latter instance a typical lacelike appearance of the cytoplasm was observed. The average height of the choroidal epithelium was 14.62 microns.

Ependyma: The subependymal tissue was somewhat loose in some places, possibly owing to edema, but the epithelium itself showed practically no vacuolization.

Comment.—The choroid plexus showed only moderate changes five days after injury. The edema of the stroma was moderate and asymmetrical. Vacuolization of the choroidal epithelium (35 per cent) was somewhat increased and the cells were somewhat heightened (14.62 microns). No signs of inflammation of the choroid plexus were made out in spite of pneumonia and death five days after injury. This picture may represent a receding condition rather than that present at the height of the cellular activity.

CASE 40.—*Compound, comminuted, depressed fracture of the skull; meningitis; death in nineteen days.*

A man, aged 52, was hit by an automobile while he was crossing the street at about 7:25 p. m. on Dec. 25, 1929. He was taken to the Emergency Hospital, and then to the White Memorial Hospital where he died at 2:25 p. m. on January 12. No detailed examination was recorded.

The coroner's examination revealed multiple contusions and lacerations of the head and extremities. The meninges were found to be somewhat cloudy and the brain was densely adherent at the tip of the left occipital and left frontal lobes to the fracture of the skull. These two areas seemed to have been severely contused and at the time of autopsy were found to be infected and disintegrating. The

cerebellum was covered with thick grayish-yellow pus. There were an extensive fracture of the base of the skull and a depressed fracture of the vault. The lungs were extensively consolidated and were found to be lightly adherent to the chest wall by recent fibrinous adhesions. The fifth, sixth and seventh ribs on the right side were found to be fractured in the anterior axillary line. The cause of death was given as meningitis following compound, comminuted, depressed fracture of the base of the skull and other injuries.

Histologic Examination.—Choroid Plexus: There was moderate edema of the stroma which involved the plexus throughout its extent. The blood vessels were open and in many instances filled with red blood cells. Of particular interest was the presence of polymorphonuclear leukocytes in the intervillous spaces of the distal tufts (fig. 16). A few "fibrin thrombi" were found throughout the plexus. The epithelial margin was irregular owing to the breaking up of the cells consequent to edematous change. The epithelial cells contained vacuoles of widely varied size, some being very large and others in the form of tiny droplets. Forty-three per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.48 microns.

Ependyma: The subependymal tissue was rather loose in structure and in one or two places the epithelium was vacuolated.

Comment.—In this case, in which death occurred from meningitis nineteen days after injury, there were evident changes in the choroid plexus. Edema of the stroma was moderate, and vacuolization of the cells was much increased (43 per cent). The choroidal epithelial cells were also heightened (15.48 microns). Inflammatory changes were present in the stroma and along the ependymal margin where many leukocytes were seen. These inflammatory changes, while definite, were not as marked as one would expect in a case of advanced meningitis.

CASE 41.—*Compound, comminuted, depressed fracture of the skull, with laceration of the brain; death in three and a half days.*

A man, aged 27, was injured about 1 a. m. on Jan. 16, 1930, when his automobile crashed into a cement wall. He sustained an extensive depressed fracture in the right frontal region, together with concussion and contusion of the brain, and he was taken to the Sylvan Lodge Hospital in a state of shock. A blood transfusion was carried out. A spinal fluid leak developed from the wound. On January 18, the depressed bone was elevated and bubbles of air came through the frontal sinus. The patient's condition remained critical and he died at 3: 10 p. m. on January 19.

The coroner's examination revealed a depressed fracture in the right frontoparietal region associated with severe hemorrhage into the tissues around both eyes. Other lacerations and contusions about the face, neck and extremities were also observed. On opening the head a severe general subdural hemorrhage and severe lacerations of the right frontal lobe of the brain were found. There was an extremely severe, depressed, badly comminuted fracture of the base of the skull involving both the middle and anterior cerebral fossae and the frontal and right parietal bones. The cause of death was given as compound, comminuted, depressed fracture of the base of the skull, with laceration of the brain.

Histologic Examination.—Choroid Plexus: Diffuse edema of the stroma was present which involved the plexus symmetrically. The blood vessels were open and in many cases were filled with red blood cells. An occasional "fibrin thrombus"

was seen and numerous psammoma bodies were encountered in the pedicle. In one or two places hemorrhagic extravasations had taken place in the base of the plexus. Coagulated fibrin and large numbers of polymorphonuclear leukocytes indicated septic meningitis (infection) (fig. 15). The epithelial margin seemed to be symmetrical. The cells contained unusually small vacuoles. Thirty per cent of the cells were vacuolated. Many of the cells showed numerous small droplets in their cytoplasm. Higher magnifications revealed an irregularity of their free margin. The average height of the choroidal epithelium was 13.76 microns. The basement membrane was irregular and distorted in many places.

Ependyma: The ependyma and subependymal tissue showed no variation from the normal.

Comment.—This case showed diffuse edema of the stroma which was symmetrical. Large areas of coagulated fibrin containing many polymorphonuclear leukocytes were found, which seemed to indicate infection. The coroner, however, did not find evidence of meningitis. The ependyma showed leukocytes attached to its margin, also indicative of inflammation.

CASE 42.—*Concussion of the brain and other severe injuries; death within an hour.*

A man, aged 67, fell down an elevator shaft at about 5:30 p. m. on Jan. 25, 1930, sustaining a fractured pelvis, multiple fractured ribs, concussion of the brain and other injuries. He was taken to the Emergency Hospital in extreme shock and died at 7:10 p. m. on the same day.

The coroner's examination showed multiple contusions and lacerations of the head, body and extremities. No fracture of the skull or free hemorrhage was found, but there was severe capillary hemorrhage throughout the brain substance and pons. In addition a left hemothorax, bilateral congestion of the lungs, multiple fractured ribs, rupture of the spleen and fracture of the pelvis were also noted. The cause of death was given as concussion of the brain, shock following injury to the head, fractured ribs, a punctured lung, hemothorax and other severe injuries.

Histologic Examination.—Choroid Plexus: There was moderate edema of the stroma which involved the plexus symmetrically. The blood vessels were full and in most cases contained red blood cells. Numerous "fibrin thrombi" and psammoma bodies were found. The epithelial cells showed a fairly regular margin and the basement membrane was intact in most places. The few vacuoles were fairly well circumscribed. Thirty-five per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.39 microns. No pigment was found.

Ependyma: No change of ependyma or subependymal tissues was seen.

Comment.—In this instance edema of the stroma was slight as would be expected when death was sudden and particularly when shock was present. Vacuolization of the choroidal epithelium was more than one would expect (35 per cent) and the height of the epithelial cells was considerably increased (15.39 microns). When one encounters such observations in conditions that seem to counteract any tendency to pressure, there must be a multiplicity of contributing factors.

CASE 43.—*Basal fracture of the skull; extradural hemorrhage with other injuries; death in six days.*

A man, aged 48, was injured at about 3:40 p. m. on Jan. 20, 1930, when he was struck by an automobile. He was transferred from an Emergency Hospital to the Los Angeles General Hospital on January 21. Examination revealed many superficial lacerations, bleeding from the left ear and fractures of the right arm and right leg. Roentgenograms showed fractures of the bones of the right leg, left elbow and left shoulder, but none of the skull. The patient died at 2:45 p. m. on January 26.

The coroner's examination revealed multiple contusions, abrasions and lacerations of the head, body and extremities. A moderate subdural hemorrhage was found over the left cerebral hemisphere and a moderate extradural hemorrhage at the base of the skull on the same side. There were multiple fractures of the base of the skull. The lungs were both massively consolidated. The sixth rib was found to be fractured in the midaxillary line. The cause of death was given as fracture of the base of the skull with extradural and subdural hemorrhage and bronchopneumonia following fracture of the ribs.

Histologic Examination.—Choroid Plexus: There was moderate edema of the plexus. The blood vessels were moderate in size and in many cases were filled with red blood cells. "Fibrin thrombi" were numerous. The free margin of the epithelium was regular in most places, although here and there individual cells seemed to be broken up by the rupture of the surface vacuoles. The vacuoles varied considerably in size and position from multiple small droplets to vacuoles that occupied almost the entire wall. Forty-one per cent of the cells were vacuolated. The average height of the choroidal epithelium was 14.36 microns. The basement membrane showed considerable distortion in many places.

Ependyma: The subependymal tissue seemed to be rather loose and in some places the epithelium was extensively vacuolated.

Comment.—Edema of the plexus was only moderate, but vacuolization of the choroidal epithelium was marked (41 per cent). The choroidal cells were moderately heightened (14.36 microns). The subependymal tissue was edematous and the epithelial cells themselves were extensively vacuolated in places. Vacuolization was rather more marked than is usually seen after the first few hours. It may be questionable whether general intracranial bleeding tended to continue the pressure.

CASE 44.—*Dislocation of the first cervical vertebra; contusion of the spinal cord; subdural hemorrhage.*

A woman, aged 42, was struck by an automobile at 10:10 p. m. on Jan. 25, 1930, while crossing the street. She was picked up dead by the police ambulance shortly afterward.

The coroner's examination showed multiple severe contusions and lacerations. There were a fracture of the left humerus and a dislocation of the right knee. A severe general subdural hemorrhage was found, but no fracture of the skull. The first cervical vertebra was dislocated and the spinal cord was contused but not severed. There were multiple fractures of the ribs with laceration of the lungs and blood in the pleural cavities. There were lacerations of the spleen, liver and left kidney with intraperitoneal and retroperitoneal hemorrhage. The cause

of death was given as dislocation of the skull on the vertebral column, with contusion of the spinal cord, subdural hemorrhage and other severe injuries.

Histologic Examination.—Choroid Plexus: Diffuse symmetrical edema of the stroma was found. There were fairly numerous "fibrin thrombi" and concretions in the stroma. The free margin of the epithelium was regular in most places. The vacuoles were moderate in size and fairly well circumscribed. Fifty-one per cent of the cells were vacuolated. The basement membrane showed but minor distortion. The average height of the choroidal epithelium was 15.05 microns. The blood vessels were moderate in size and in many instances contained red blood cells.

Ependyma: No vacuolization was present in the ependyma nor was any subependymal edema found.

Comment.—In spite of the fact that this patient apparently died within a few minutes of the time of injury, there was diffuse symmetrical edema of the stroma with a marked increase of vacuolated cells (51 per cent). The vacuoles, however, were moderate in size and well circumscribed. Several large cells measuring more than 26 microns were found. The average height of the cells was 15.05 microns. No essential change in ependyma or subependymal tissue was seen. The occurrence of fairly marked changes in the plexus in cases of immediate death suggests the possibility of some postmortem activity of the plexus. We see no other way to explain the occurrence.

CASE 45.—*Concussion of the brain; dislocation of the fifth cervical vertebra; death in forty-one hours.*

A man, aged 21, was injured in an automobile accident at 11 p. m. on Jan. 24, 1930, and was brought to the Los Angeles General Hospital on January 25. He was rendered unconscious at the time of injury, but soon recovered consciousness. Clinically he showed signs of cervical injury to the spinal cord. Roentgenograms showed displacement of the fourth cervical vertebra on the fifth, or vice versa. The patient died about 4 p. m. on January 26.

The coroner's examination showed a few small, moderately severe contusions of the right side of the head and face, a small contused abrasion of the back of the right shoulder, and a similar small contusion of the left shin. No fracture of the skull, hemorrhage or injury to the brain was found. By dissecting the soft parts away from the front of the vertebral column the fourth cervical vertebra was found to be dislocated forward on the fifth cervical vertebra. The cause of death was given as dislocation of a cervical vertebra, with injury to the spinal cord.

Histologic Examination.—Choroid Plexus: The plexus showed a moderate degree of edema which was symmetrical in distribution. The blood vessels were empty and not dilated. Numerous small "fibrin thrombi" were found throughout the field. The epithelium showed a fairly regular outline with little alteration in the morphology of its cells. Many of the cells were small, although some of them reached large proportions. Forty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.82 microns.

Ependyma: The subependymal tissue seemed to be rather loose in some places and a moderate degree of vacuolization was present throughout its extent.

Comment.—This case, in which an injury to the cervical cord was the prime cause of death, is included because the patient also sustained

a concussion of the brain, being unconscious for several hours. He probably would have recovered had the concussion been the only injury. There were moderate edema of the stroma and a considerable increase of vacuolization of the choroid (44 per cent). The choroidal epithelium cells were definitely heightened (15.82 microns). Many nonfatal cases of concussion probably have as many changes in the choroid plexus and ependyma as is shown in this instance, for the head injury itself would correspond to the conception of mild concussion. Hypertonic dextrose solution was not given. This perhaps accounted for the comparatively marked evidence in the choroid.

CASE 46.—*Concussion of the brain; subdural hemorrhage; a crushed chest; death in three hours.*

A man, aged 72, was injured at 6:30 a. m. on Jan. 28, 1930, in an automobile collision, and was taken to the Emergency Hospital where he died about three hours later. He showed signs of internal injuries to the chest and abdomen, as well as a possible fracture of the skull, subdural hemorrhage and marked shock.

The coroner's examination showed multiple lacerations, abrasions and contusions of the head, body and extremities. No fracture of the skull or injury to the brain was found, but there was moderate subdural hemorrhage over the right occipital lobe of the brain. A retrosternal hemorrhage was found. All the ribs on the right side were fractured, each in a number of places; in their posterior portions they were severely splintered and had lacerated the lung severely. The spleen showed a small rupture and the liver several contusions. The cause of death was given as injury to the head with concussion of the brain and subdural hemorrhage, and multiple fractures of the ribs with laceration of the lung.

Histologic Examination.—Choroid Plexus: There was practically no edema of the stroma. The blood vessels were of average size and empty. Little vacuolization of the choroid epithelium was found and the basement membrane was essentially intact. Vacuolization occurred in 28 per cent of the cells, and the average height of the choroidal epithelium cells was 11.18 microns.

Ependyma: The ependyma nearest the choroid plexus was moderately vacuolated.

Comment.—In spite of the fact that an interval of three hours elapsed between injury and death in this case, there were no changes in the choroid plexus or ependyma worthy of mention. The extensive injuries to the lungs, spleen and liver may have accounted for the patient's death, instead of the injury to the brain which may well have been relatively trivial. Furthermore, the age of the patient and shock probably prevented more marked changes.

CASE 47.—*Fracture of the skull, with subdural hemorrhage; death in about two weeks.*

A man, aged 62, was admitted to the Los Angeles General Hospital on Jan. 27, 1930, with a history of having been struck on the back of the head two weeks previously. Examination showed fracture of the skull and course râles throughout the chest. All the reflexes were increased and a bilateral Babinski sign was present. The patient died on January 28.

The coroner's examination revealed a few discolored areas on the back of the shoulders, arms and thorax, which were superficial. A large subdural hemorrhage covered the posterior half of the right hemisphere of the brain, the blood being thin and fluid. There was a fracture running from the internal occipital protuberance forward into the opening of the spinal canal. The cause of death was given as fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Extensive edema of the stroma was found which seemed to be diffuse and involved the choroid plexus throughout its extent. The fluid spaces were usually small. "Fibrin thrombi" and psammoma bodies were numerous. The choroid epithelium showed numerous vacuoles, some of which contained pigment; 40 per cent of the cells were vacuolated. The average height of the choroidal epithelium was 16.85 microns. The basement membrane was distorted and compressed in some places. Hemorrhagic extravasation was present in the base of the pedicle.

Ependyma: No subependymal edema or vacuolization of the ependyma was observed.

Comment.—A fairly extensive edema of the choroid stroma was found, together with increased vacuolization (40 per cent) and heightening (16.85 microns) of the epithelial cells. From the fact that such diffuse changes were still present in the choroid two weeks after injury, it is evident that cerebral edema may persist over a period of weeks, especially if untreated. In contrast to this are cases in which energetic treatment with hypertonic dextrose solution was given; these showed minor changes in the choroid, death being brought about by other causes.

CASE 48.—*Basal fracture of the skull; subdural hemorrhage; death in eleven days.*

A man, aged 59, was found lying unconscious on the sidewalk, bleeding from a wound on the left side of the scalp, at about 7 p. m. on Jan. 14, 1930. He soon regained consciousness. Except for periodic twitching of the right side of his face he progressed fairly well until the evening of January 19; then terrific headaches developed and at times the patient became drowsy. He was taken to the California Hospital where the results of neurologic examination were essentially negative. A lumbar puncture revealed a very bloody spinal fluid under 200 mm. of pressure. Roentgenograms of the skull revealed a linear fracture in the left temporal region. On January 22, marked cerebrospinal rhinorrhea developed and the headaches increased. At operation on the evening of January 22 a large amount of bloody spinal fluid was removed and a soft rubber drain was placed under the left temporal lobe. The following morning the cerebrospinal rhinorrhea had stopped. The patient became worse, however, and died on January 25, at 4:55 p. m.

The coroner's examination showed that the vault and base of the skull were fractured on the left side. A decompression had been performed and no hemorrhage was found at the time of autopsy. There were two small distinct areas of contusion of the right middle lobe of the brain. The left eye showed ecchymosis and there was a contusion on the right knee. The cause of death was given as fracture of the base of the skull.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was found which seemed to be more marked in some places than in others. Scattered here and there in the intervillous spaces were little groups of leukocytes and fibrin which suggested an inflammatory process. A few "fibrin thrombi" and psammoma bodies were found. The epithelium showed irregularity of its free margin owing largely to the prominence of the individual cells, but in a minor degree also to a breaking up of the distal margins. Many of the cells were vacuolated, containing various-sized, clear spaces, only a few of which reached unusual proportions. Fifty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 14.89 microns. The basement membrane showed moderate changes in its contour. A few leukocytes were found in the edematous stroma.

Ependyma: The ependyma showed vacuolization in some areas, but did not differ widely from the normal in appearance.

Comment.—This case showed areas of inflammatory reaction in the free ventricle shown by leukocytes in its cavity. The vacuolization of the choroidal epithelium was much increased (54 per cent) and a few leukocytes were found in the edematous stroma. In spite of these histologic changes no gross reaction was noted by the coroner. As little evidence of hemorrhage or damage to the brain was found, it is likely that edema played an important part in the clinical picture. To a lesser degree inflammatory changes may have contributed to the patient's death.

CASE 49.—*Subdural and extradural hemorrhage with fracture of the skull and internal injuries; death in thirty-two hours.*

A woman, aged 45, was injured in an automobile collision about 6:50 p. m. on Jan. 13, 1930. She was rendered immediately unconscious and remained so until her death. There were clinical signs of fracture of the skull with a subdural hemorrhage and fracture of the left clavicle, ulna and radius, as well as multiple fractures of the ribs. She died at the Emergency Hospital at 2:27 a. m. on January 15.

The coroner's examination revealed multiple contusions and lacerations of the head, body and extremities. The left clavicle and both bones of the left forearm were broken. A large extradural hemorrhage was found on the left side of the head with severe compression of the entire left cerebral hemisphere; there was severe general subdural hemorrhage and slight contusion of the under surface of the brain. There were extensive comminuted basal fractures of the skull in both posterior cranial fossae, in the left middle fossa and through the cribriform plate. There were multiple fractures of the ribs on the left side associated with laceration of the left lung and hemothorax. The right lung was severely contused and the lower lobe showed an early consolidation with a fibrinopurulent exudate on its surface. The cause of death was given as subdural and extradural hemorrhage following comminuted basal fracture of the skull and other severe injuries.

Histologic Examination.—Choroid Plexus: There was a moderate diffuse edema of the stroma which seemed to involve all portions of the plexus alike. The blood vessels were open and in most cases empty. The pedicle had been filled with fluid so that it presented nearly netlike septums separated by wide fluid spaces. The solid connective tissue masses were studded with psammoma bodies. The

epithelium of the distal tufts was regular. The basement membrane was fairly well preserved. Vacuolization occurred in 37 per cent of the cells. The vacuoles were not markedly increased in number and varied in size within fairly wide limits. The average height of the choroidal epithelium was 13.58 microns.

Ependyma: The subependymal tissue seemed to be fairly solid and the epithelium showed no vacuolization except in a few circumscribed locations.

Comment.—This case showed moderately diffuse edema of the stroma of the choroid plexus as well as increased vacuolization (37 per cent) of the choroidal epithelium which was moderately heightened (13.58 microns). The ependyma and subependymal tissue showed little change. From the coroner's observations it seemed evident that intracranial hemorrhage and shock rather than cerebral edema were the chief factors in bringing about the patient's death.

CASE 50.—*Basal fracture of the skull, subdural hemorrhage and internal injuries; death in one hour.*

A woman, aged 50, was hit by an automobile while crossing the street at about 7:55 p. m. on Jan. 29, 1930. She was taken to the Emergency Hospital, where she was found to have sustained a fracture of the base of the skull, a crushed chest, a fractured pelvis and other internal injuries. She died an hour later.

The coroner's examination revealed severe contusions and abrasions of the head, trunk and extremities as well as a fracture of the left clavicle and pelvis. A severe subdural hemorrhage was found over the entire right cerebral hemisphere, with compression and pushing of the hemisphere toward the opposite side. There was an extensive fracture of the base of the skull on the left side involving the left middle cerebral fossa and the left vault. The second to seventh ribs, inclusive, on the left side of the chest were fractured with hemorrhage into the left pleural cavity. The diaphragm was torn on the left side and the stomach protruded through into the pleural cavity. The cause of death was given as fracture of the base of the skull, with subdural hemorrhage and other severe injuries.

Histologic Examination.—Choroid Plexus: There was marked balloon-like distention of the plexus which involved its entire structure. The blood vessels were not particularly prominent and in most instances were empty. "Fibrin thrombi" were numerous throughout the section. The entire stroma seemed to be broken up by the increase in fluid which was particularly marked in the large pedicle of the plexus. In the ventricular space there was a certain amount of free blood and coagulated fibrin. The free epithelial margin was inclined to be irregular owing both to the enlargement of individual cells and to the rupture of small distal vacuoles. The epithelial cells contained numerous vacuoles, many of which were large and, in some cases, unusual in size. Fifty-six per cent of the cells were vacuolated. The average height of the choroidal epithelium was 17.20 microns. The accumulation of fluid in the space between the blood vessels and the epithelium so distorted the structures in most places that the basement membrane could not be seen clearly.

Ependyma: The ependyma was vacuolated practically throughout its extent, although more marked in some places than others.

Comment.—This case presented "full blown" changes in the choroid plexus. The stroma was ballooned out, vacuolization of cells was high

(56 per cent) and the cells were increased in size (17.20 microns). The ependyma also showed marked vacuolization. The association of these marked changes with extensive intracranial hemorrhage and other severe injuries occurring in such a short period seems unusual.

CASE 51.—*Basal fracture of the skull, contusion of the brain and internal injuries; death within one hour.*

A man, aged 25, fell from the fifth story of a building at 5:27 p. m. on Feb. 6, 1930. He was taken to the Emergency Hospital where he showed signs of extensive internal injuries as well as fracture of the base of the skull. He died at 6:15 p. m.

The coroner's examination revealed extensive and marked abrasions, contusions and lacerations involving all parts of the body. The left wrist was partially dislocated. A severe subdural hemorrhage was found over the entire right cerebral hemisphere, with severe contusion. An extensive fracture of the base of the skull was found which involved the left middle fossa, the region of the sella turcica and the cribriform plate. The first nine ribs on the left side were fractured near their middle and the left pleural cavity contained about 1 quart (946 cc.) of free blood. Both lungs were lacerated. The cause of death was given as fracture of the base of the skull, with contusions of the brain, subdural hemorrhage and other severe injuries.

Histologic Examination.—Choroid Plexus: Rather extensive edema was found which involved the plexus more or less symmetrically. The blood vessels were not particularly distended and most of them were empty. Fluid spaces formed a conspicuous feature. "Fibrin thrombi" were fairly common and there were numerous psammoma bodies in the pedicle of the plexus, some of which had reached a tremendous size. The epithelium showed considerable variation in its reaction to the swelling of the stroma. In some places the cells appeared vacuolated, but for the most part little change from the normal was observed; 28 per cent were vacuolated. The vacuoles were small and well outlined. The average height of the choroidal epithelium was 13.24 microns. The basement membrane was frequently distorted and torn by the underlying fluid.

Ependyma: In some locations there was a definite accumulation of fluid in the subependymal tissues over which the epithelium was tremendously distorted.

Comment.—This case showed extensive edema of the choroid plexus, but only moderate vacuolization and little increase in the height of the cells. The ependyma showed more changes than did the choroid plexus. It may be that edema occurs first in the plexus and is followed by activity of the epithelial cells later, at least under certain conditions.

CASE 52.—*Subdural hemorrhage; fractured right femur; death in six days.*

A man, aged 89, was struck by a bus at 8:30 a. m. on Feb. 3, 1930. He was sent to the Emergency Hospital and was transferred to the Los Angeles General Hospital where he died at 11:50 p. m. on February 9. The right femur was fractured. Bronchopneumonia developed from which the patient died.

The coroner's examination revealed a fracture through the neck of the right femur with external rotation of the distal fragments. An excess of cerebrospinal fluid was found; over the left cerebral hemisphere the brain and dura were markedly stained by changed blood from an old hemorrhage (one week or ten days). No fracture of the skull was found. The dependent portions of both

lungs were consolidated and friable, presenting the picture of a well consolidated hypostatic pneumonia. The cause of death was given as hypostatic pneumonia following fracture of the right femur.

Histologic Examination.—Choroid Plexus: Rather marked edema of the stroma was present. The blood vessels were dilated and empty. The free margin of the epithelium was slightly irregular owing largely to unequal swelling of the cells. The vacuoles varied in size, although those of unusual proportions were rare. Thirty-seven per cent of the cells were vacuolated. The average height of the choroidal epithelium was 13.24 microns. The basement membrane was fairly well preserved.

Ependyma: The subependymal tissue showed little localized evidence of fluid. Vacuolization was present to a marked degree in one locality only.

Comment.—At the end of six days this patient showed marked edema of the stroma and considerable vacuolization (37 per cent). The cells averaged 13.24 microns in height. This patient was the oldest in the series. The choroid plexus did not show inflammatory changes as have frequently been seen several days after injury. The cause of increased vacuolization so long after injury is not clear.

CASE 53.—*Fracture of the skull; subdural hemorrhage; ruptured liver; death in six days.*

A man, aged 63, was injured in an automobile accident at 8:30 a. m. on Feb. 3, 1930, and was admitted to the Los Angeles General Hospital where he died at 12:25 p. m. on February 9.

The coroner's examination revealed a laceration and contusion in the right temporal region, a contusion of the right eye, an abrasion on the right cheek, and contusions on the other side of the right arm and on both knees. A subdural hemorrhage over the base and lateral surface of the left temporal lobe of the brain was found associated with a fracture of the right parietal region and the right anterior and middle fossae. The liver was ruptured in six places, the gallbladder was also ruptured, and all the abdominal viscera were stained with bile. The cause of death was given as fracture of the base of the skull with rupture of the liver and gallbladder.

Histologic Examination.—Choroid Plexus: Rather marked edema of the stroma was found which involved the entire plexus. "Fibrin thrombi" were numerous and occasional psammoma bodies were found in the pedicle. The blood vessels were moderate in size and most of them were empty. The free margin of the epithelium was irregular, owing to marked vacuolization of the cells. Sixty-four per cent of the cells were vacuolated. For the most part, the vacuoles were uniform in size although some were large enough to occupy the larger portion of the cytoplasm. The average height of the choroidal epithelium was 15.99 microns. The basement membrane varied in regularity, although in most places it was definitely distended.

Ependyma: A marked increase in the vacuolization of the ependyma was observed, particularly in the region where it becomes continuous with the epithelium of the choroid plexus. The subependymal tissues showed little alteration.

Comment.—At the end of six days this case showed marked edema of the stroma and high vacuolization of the cells (64 per cent). The choroidal epithelium was heightened (15.99 microns). The changes

here were about as marked as are ever seen in the "full blown" cases in which death occurs in from two to four hours.

CASE 54.—*Basal fracture of the skull; subdural hemorrhage and contusion of the brain; death within one hour.*

A boy, aged 12, was injured in an automobile collision at 7 p. m. on Feb. 8, 1930, and died before he arrived at the Emergency Hospital.

The coroner's examination revealed severe and extensive superficial injuries of the head, body and extremities. A severe general subdural hemorrhage and a contusion of the right cerebral hemisphere were found. There was an extensive fracture of the base of the skull, involving all the cerebral fossae on the right side and the middle fossa on the left. The cause of death was given as fracture of the base of the skull, with a subdural hemorrhage and a contusion of the brain.

Histologic Examination.—Choroid Plexus: There was moderate edema of the entire plexus. A localized hemorrhagic extravasation was seen in one portion of the pedicle associated with pigmentation in the regional cells. No "fibrin thrombi" or calcospheres were present. Viewed under low power magnification, the choroidal epithelium seemed fairly regular, but under higher magnifications the distal portions of the cells were seen to be serrated. Vacuolization of these cells was not extensive, 50 per cent of the cells being so involved. The average height of the choroidal epithelium was 14.27 microns. The basement membrane was fairly well preserved in most places. No pigment was present except in the region of the hemorrhagic extravasation.

Ependyma: Some looseness of the subependymal tissues was found associated with vacuolization which was marked in one or two extensive stretches.

Comment.—In spite of the short time that elapsed from the time of injury until death (less than one hour), this case showed moderate edema of the stroma of the choroid plexus and 50 per cent of the cells were vacuolated. The subependymal tissue was also loose and the epithelial cells considerably vacuolated.

CASE 55.—*Concussion of the brain; a ruptured bladder; death in nine days.*

A woman, aged 36, was injured in an automobile accident on Jan. 19, 1930, and was unconscious for twenty-four hours. A ruptured bladder was found on abdominal exploration. Roentgenograms revealed multiple fractures of the ribs, a fractured pelvis and pleural effusion on the day of the patient's death, January 28.

The coroner's examination showed multiple contusions of the body and extremities. A large accumulation of blood was found beneath the scalp over the right parietal region. No fracture of the skull, injury to the brain or intracranial hemorrhage was found. All the ribs on the right side as well as two on the left were fractured near their vertebral ends with laceration of both lungs and hemothorax. The left side of the diaphragm was ruptured, and a large portion of the spleen and part of the splenic flexure of the colon protruded through into the left pleural cavity. The bladder showed a recently sutured opening in the front with a self-retaining catheter sutured in place and extending out through the surgical wound in the abdomen. The bladder was contracted and contained a great deal of thick, purulent looking material. The right sacro-iliac articulation was fractured. The cause of death was given as multiple fractured ribs with lacerated lungs, hemothorax and other severe injuries.

Histologic Examination.—Choroid Plexus: A minor degree of edema of the stroma was present and the blood vessels were open and empty, 30 per cent of the cells being vacuolated. The choroidal epithelium was regular; the vacuoles were small. The average height of the choroidal epithelium was 12.38 microns. The basement membrane was fairly well preserved throughout. Occasional "fibrin thrombi" were seen.

Ependyma: No subependymal accumulations of fluid were present. The ependymal lining was vacuolated only to a moderate degree.

Comment.—As would be expected from the coroner's report the injury to the head was relatively minor in comparison with other internal injuries. The choroid plexus showed little change from the normal. It is likely that similar changes occur in many persons with concussion who recover.

CASE 56.—*Basal fracture of the skull; laceration of the brain and internal injuries; death within an hour.*

A man, aged 25, fell from a building at 9:30 a. m. on Feb. 8, 1930, and was picked up dead by the police ambulance attendants shortly afterward.

The coroner's examination revealed multiple severe contusion, abrasions and lacerations covering the head, body and extremities. There were fractures of the right clavicle, small bones of the right hand and right femur, together with dislocation of both hip joints. Severe contusions and lacerations of various portions of the brain and cerebellum were found, but there was only moderate hemorrhage. There was a severe comminuted fracture of the entire base of the skull. All the ribs on the right side and four on the left side were fractured and a fractured dislocation of the tenth and eleventh dorsal vertebrae was found. Both lungs were lacerated and free blood was present in the pleural cavity. The left side of the diaphragm was ruptured and the spleen and the splenic flexure of the colon protruded into the pleural cavity. The liver and kidneys were torn and there was much free blood in the abdominal cavity. There was a complete fracture of the ileum on each side of the sacrum. The cause of death was given as fracture of the base of the skull with lacerations of the brain and other severe injuries.

Histologic Examination.—Choroid Plexus: Extensive edema of the stroma was found which involved the entire plexus. There were occasional "fibrin thrombi," but no psammoma bodies were seen. The blood vessels were moderate in size and many still retained red blood cells. Various-sized fluid spaces were found scattered throughout the stroma. The free margin of the epithelium was irregular in some places, evidently owing to rupture of tiny vacuoles. The epithelial cells were not markedly vacuolated (30 per cent). The average height of the choroidal epithelium was 12.54 microns. The vacuoles present were small. The basement membrane seemed to be well preserved, except over large accumulations of fluid.

Ependyma: The ependyma everywhere retained its normal morphologic aspects.

Comment.—In spite of the short time elapsing between injury and death, extensive edema of the choroid plexus stroma was evident, but vacuolization of the cells and heightening of the choroidal epithelium were not marked. Probably edema of the stroma begins before vacuolization of the choroidal epithelium appears. This is to be expected if fluid from the stroma passes into the epithelial cells.

CASE 57.—*Subdural and petechial hemorrhages of the brain; gas bacillus infection of the arm; death in nine days.*

A youth, aged 18, went over a cliff in an automobile on Feb. 2, 1930. He fractured the right arm and was in deep coma until February 11, on which day the gas bacillus was found in a culture and the patient died.

The coroner's examination disclosed bruising around the inner corner of the right eye and a compound, comminuted fracture of the right humerus. This fracture was infected and pus exuded from a wound in the arm. There was a fracture of the right femur and a large abrasion of the anterior portion of the thigh. No fracture of the skull was found, but there were the remains of a moderate subdural hemorrhage and the brain showed severe contusions and diffuse hemorrhage throughout. The first four and the sixth ribs on the right side were fractured and both lungs showed severe general contusions, subpleural laceration and localized consolidation. The cause of death was given as pneumonia following laceration of the lungs and contusion of the brain from injury to the head.

Histologic Examination.—Choroid Plexus: Minor changes were present in the stroma of the plexus. In many localities the tufts retained their normal morphologic appearance. The blood vessels were small and empty. Only an occasional "fibrin thrombi" and no psammoma bodies were found. The epithelial margins were practically normal in outline. Only a few vacuoles were found in the epithelial cells and those were small. Thirty-three per cent of the cells were vacuolated. The average height of the choroidal epithelium was 11.78 microns. The only abnormality of the epithelial cells was the occasional occurrence of small vacuoles in the distal end of the cell. The basement membrane had been fairly well preserved.

Ependyma: Aside from a few scattered vacuoles the ependyma showed nothing abnormal.

Comment.—This patient died of a gas bacillus infection of the arm and pneumonia nine days after injury. The brain showed marked petechial hemorrhages but the choroid plexus presented only moderate changes. The ependyma likewise showed practically no change.

CASE 58.—*Basal fracture of the skull; death in twenty-seven hours.*

A man, aged 47, was injured at 2 p. m. on Dec. 10, 1927, in an automobile collision. He was taken to the Emergency Hospital where he died at 5:30 p. m. on December 11.

The coroner's examination revealed lacerations and contusions of the scalp, face and extremities. On opening the head a fracture was found running from the posterior right floor of the right middle fossa, and the roof of both orbits of the eyes was slightly fractured. On opening the body the lungs were found to be deeply congested and contused in several areas. The cause of death was given as fracture of the base of the skull.

Histologic Examination.—Choroid Plexus: Extensive edema of the plexus stroma was present; it was diffuse in some places while in others the fluid seemed to have collected in large spaces. So-called "fibrin thrombi" were present but not numerous. The blood vessels were moderate in size and empty. The choroidal epithelium showed an increase in the number of vacuoles, but these were not large. Forty-four per cent of the cells were vacuolated, many of the vacuoles containing pigment. Some pigment in fine granules was also found in the stroma. The average height of the choroidal epithelium was 13.58 microns. The basement membrane was irregular and torn in most places.

Ependyma: The subependymal stroma was looser than usual and the ependymal epithelium was moderately vacuolated, especially adjacent to the area in which it became continuous with the choroid plexus.

Comment.—This case showed a rather extensive edema of the choroid plexus stroma, with a moderate increase in vacuolization (44 per cent). The choroidal epithelium cells were moderately heightened (13.58 microns). A moderate increase in the subependymal edema and increased vacuolization of the ependymal cells were also present.

CASE 59.—*Basal fracture of the skull; concussion and contusion of the brain; death in three days.*

A man, aged 61, was injured in an automobile accident at 8 a. m. on Dec. 10, 1927. He was rendered unconscious immediately and never regained consciousness. The bones of the left leg were fractured. On December 12, a right subtemporal decompression revealed a tight, dry brain. He died at 6:20 a. m. on December 13.

The coroner's examination showed extensive lacerations of the scalp. A fracture was found running from the occipital protuberance forward through the outer part of the left half of the occiput, across the left petrosal bone at its outer end and extending by two lines across the floor of the left middle fossa of the skull. The anterior portion of the right anterior lobe of the brain and the lateral surface of the left posterior lobe were contused and lacerated. A decompression operation had been performed on the right side. The left leg and the third to the sixth ribs on the left side were fractured. The cause of death was given as fracture of the base of the skull with other injuries.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was present. The blood vessels were empty and not unusually distended. Throughout the field numerous "fibrin thrombi" were found. The free epithelial margin was not unduly irregular. A small amount of free blood was seen in the intervillous spaces. The epithelial cells contained various-sized vacuoles, some of which contained pigment. Thirty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 13.41 microns. The basement membrane was fairly well preserved in most places.

Ependyma: The ependyma showed no increase in vacuolization and appeared normal throughout its extent.

Comment.—In spite of death after three days, the choroid plexus and ependyma showed little change. From the clinical course one would look for much more marked changes at this time. The tight, dry brain at the time of operation gave evidence that an excess of cerebrospinal fluid was not present in the form of edema. It would seem that cerebral edema accompanies an increase in the activity of the choroid plexus.

CASE 60.—*Basal fracture of the skull, with subdural hemorrhage and fractured pelvis; death within one hour.*

A man, aged 40, was struck by an automobile at 1:55 p. m. on Dec. 12, 1927. He was picked up dead within a few minutes.

The coroner's examination revealed lacerations and abrasions of the scalp and face, associated with orbital hemorrhage. A fracture was found running along

the midline of the occiput into the foramen magnum, also a fracture of the roof of the right orbit. There was extensive subdural hemorrhage on the left side of the brain. On opening the body the left ramus of the pubic bone was found to be fractured, with laceration of the adjacent soft tissues. The cause of death was given as fracture of the base of the skull with fracture of the pelvis.

Histologic Examination.—Choroid Plexus: Moderate diffuse edema was found involving the stroma of the entire plexus. The blood vessels were open and empty. A few "fibrin thrombi" were found here and there in the section and a large number of psammoma bodies were found in the pedicle of the plexus. The free margin of the epithelium was irregular owing chiefly to enlargement of the individual cells. In some the distal portion of the cell assumed a lacelike appearance owing to the presence of numerous fine droplets. The vacuoles were fairly numerous and many of them contained a brownish, granular pigment. Forty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.05 microns. The basement membrane in many places could not be clearly made out because of the accumulation of fluid beneath the epithelium.

Ependyma: The ependyma showed no deviation from its normal morphologic appearance.

Comment.—This case showed moderate diffuse edema with increased vacuolization of the cells (44 per cent). The vacuoles in this instance were very small and numerous. Perhaps that is the way vacuoles form, i. e., by the coalescence of small droplets. The latter predominated in this case. It is also possible that when the activity is greatest the fluid passes through in the form of small droplets, a true cellular edema.

CASE 61.—*Basal fracture of the skull with subdural hemorrhage; death in twenty-two hours.*

A man, aged 47, was injured at 8:30 a. m. on Nov. 16, 1927, in an automobile collision. He was momentarily unconsious, but recovered consciousness later and was able to talk. After eight hours he became drowsy, the right pupil was dilated and Cheyne-Stokes respiration set in with deep coma. Roentgenograms showed a linear fracture on the right side. A right subtemporal decompression was performed and a subdural hemorrhage drained. He died at 6:25 a. m. on November 17.

The coroner's examination showed an extensive contusion of the scalp behind and above the right ear. A large subdural hemorrhage was found covering the surface of the right anterior hemisphere of the brain and an extradural clot in the right middle fossa of the skull. There was a comminuted fracture in the floor of the right middle fossa extending across the body of the sphenoid bone and also upward to the opening made by the decompression. The cause of death was given as comminuted fracture of the base of the skull.

Histologic Examination.—Choroid Plexus: A moderate generalized edema of the stroma was present. The blood vessels were open and empty. Coarse granular pigment was found throughout the section and was practically confined to the epithelium. The free margin of the epithelium almost everywhere presented a dentate appearance owing to a swelling of the distal portion of certain cells. The vacuoles were not abundant but were fairly large; most of them contained granular pigment. Thirty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.60 microns. The detail of the basement membrane seemed to be lost in most places owing to the increase in fluid in the connective tissue stroma.

Ependyma: There was an accumulation of fluid in the subependymal tissue and for a short distance the ependyma was definitely vacuolated. A small amount of coarse granular pigment was found in the ependymal cells. There was some accumulated débris on the ependyma, apparently in the nature of degenerating red blood cells. This seemed to be emphasized by the fact that black pigment was present, some of which was contained within macrophages. Furthermore, the ependymal cells in these regions seemed to be distorted and the detail was obscured by the presence of this débris as well as subependymal fluid.

Comment.—In this case a large subdural hemorrhage was found at operation. The choroid plexus showed a moderate increase in edema and vacuolization. The ependyma showed marked blood pigment being taken up by macrophages, a picture suggestive of Essick's [19] work.

NORMAL CHOROID PLEXUS

The normal choroid plexus (fig. 1), as studied in the ten patients who died of conditions that were remote and in no way influenced the central nervous system, was found to agree in practically all respects with the accepted descriptions of this structure. While the cells showed some variation in height (from 8 to 12 microns) in different portions of the plexus, such as the terminal tufts as compared with the pedicle, in similar areas they were uniform in size and showed only a slightly irregular free margin (fig. 2). It was generally observed that the cells were higher in children than in adults. The structure of each cell was typical, being columnar with a slightly rounded free distal end and a flattened proximal end lying on the basement membrane. The oval nucleus was found in the proximal portion of the cell with its long axis parallel to the long diameter of the cell. The nuclei were uniform in size and had a distinct nuclear membrane and an abundant, evenly distributed chromatin content. The cytoplasm of the cell was finely granular, the granules being evenly distributed in all portions of the cell. We found no evidence of a division into a basilar granular zone and a distal clear zone as described by Pettit and Girard.[20] Vacuoles were present in from 10 to 22 per cent of the cells; they were usually small and sharply outlined and lay in apposition to the nucleus. Occasionally, small brownish-black pigment granules were found in the vacuoles. The basement membrane appeared as a well defined, even line which separated the cytoplasm of the cell from the subjacent stroma. It is not unlikely that this is formed of a heavy cell wall rather than being an additional structure. The stroma consisted of a few strands of connective tissue lying between the basement membrane and the blood

19. Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulus of Particulate Matter, Contrib. Embryol., no. 42, Washington, Carnegie Institution, 1920.

20. Pettit and Girard (footnote 7, second reference).

vessel. Nuclei of connective tissue cells were found in small numbers in this stroma. The blood vessels in the terminal tufts were small and capillary in nature, being formed of endothelial cells. In most instances they were empty and round, evidently owing to the previous embalming.

We have noticed that in general the older the subject the more likely it is to find psammoma bodies or calcospheres, which usually occur in the pedicle of the plexus. They probably correspond to the so-called "fibrin thrombi," irregular masses of fibrinous material in the blood vessels of the tufts of the plexus. Such masses are shown to contain

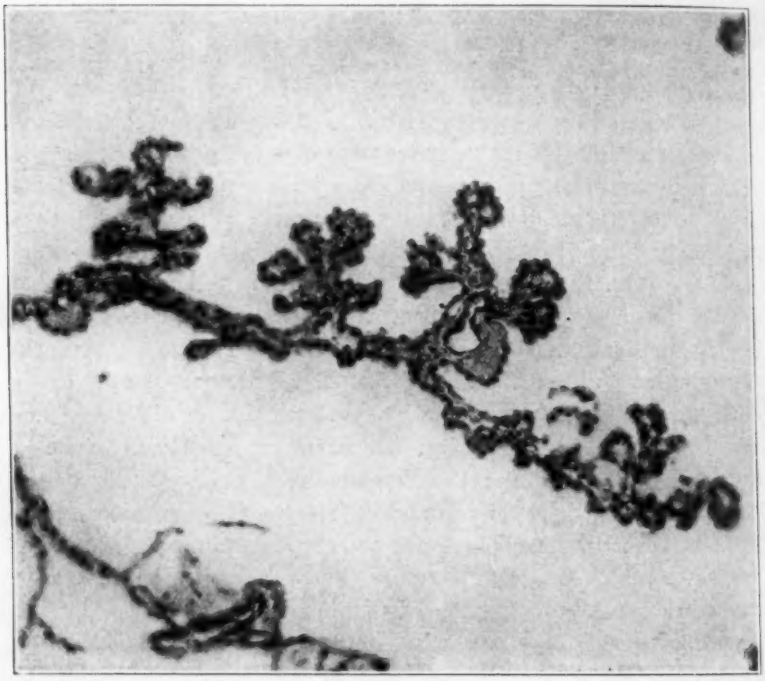

Fig. 1.—Normal choroid plexus. The connective tissue stroma forms an inconspicuous part of the structure. Consequently, the epithelial cells on either side of the villus are practically in apposition, except where separated by blood vessels. Hematoxylin and eosin; reduced from × 200.

iron by the Prussian blue method. We believe that they have nothing to do with the injury to the head, but that they are evidence of a regressive change in the plexus, the causes of which are not clear.

HISTOPATHOLOGIC CHANGES

Definite changes have been found in practically all the constituents of the choroid plexus following trauma. In general the free epithelial

margin has shown greater irregularity in outline than is seen in that of a normal choroid plexus. In places the free border appears regularly serrated, owing perhaps to the increased height of the individual cells (fig. 3). This increase in height is thought to be due to an accumulation of fluid in the cell. It may represent edema of the cell, or may take the form of discrete vacuoles. Less commonly the free epithelial margin is actually ragged and torn. This is due to an actual destruction or tearing of the free margin, and not infrequently tags of cytoplasm may be seen swimming free in the ventricular space. These

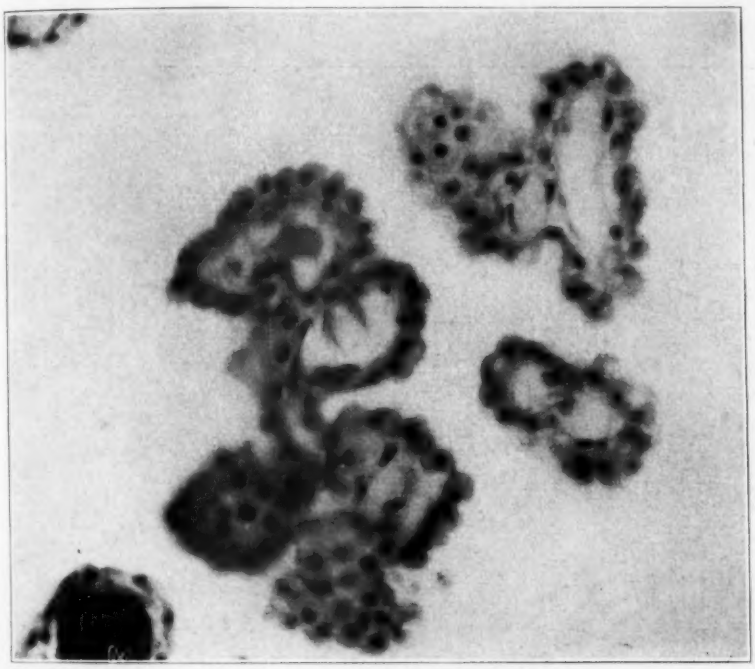

Fig. 2.—Normal choroid plexus. The connective tissue is confined to a few small compact strands lying between the basement membrane and the wall of the blood vessel. A few vacuoles are seen in the epithelial cells. Hematoxylin and eosin; reduced from × 680.

fragments may become detached and rounded, and may resemble the so-called "hyaline bodies" which some writers have described as occupying the space adjacent to the free margin. We have not observed any true hyaline bodies, but have seen these rounded structures which we could not distinguish morphologically from red blood cells. The free margin is more apt to be ragged, with numerous small vacuoles rupturing through it into the ventricle, than showing a single large vacuole. The latter, however, may give a torn appearance if it breaks

through the margin. In view of the work of Pettit and Girard,[21] as well as that of Meek [22] and others who described a marginal clear zone and a basal granular zone in what they considered to be actively secreting choroid epithelium, we have looked for similar observations in this series. However, we have rarely, if ever, observed this lack of granules in the apical part of the cells. In only one instance did it seem to be present, but in this case the edge, although lighter, was ragged as though it had been broken up with apparent loss of the smooth free margin of the cell.

Careful measurement of cells in certain areas was made in every case in this series. They differed greatly in height. In various cases

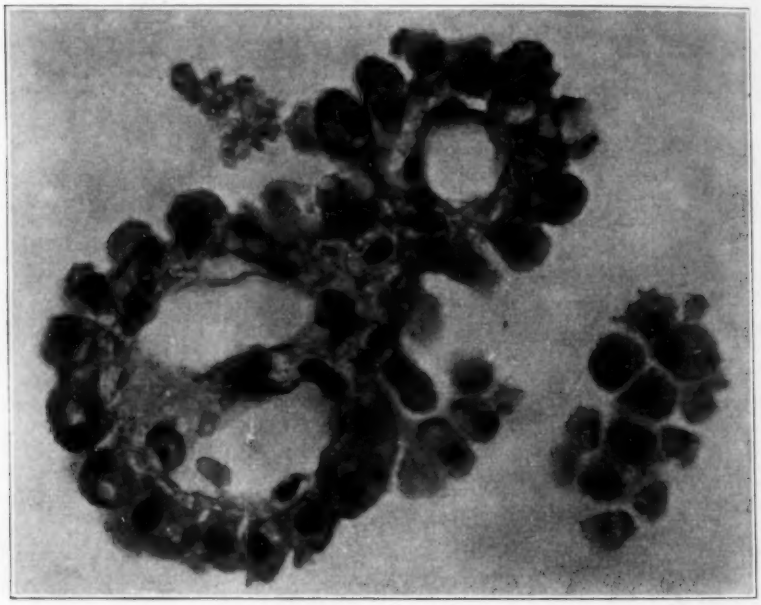

Fig. 3.—Vacuolization and serrated appearance of choroidal epithelium in case 3. There is an increase in the number of vacuoles in the epithelial cells. Some are also seen between the cells and along the basement membrane. At the upper right, one large cup-shaped vacuole is seen rupturing into the ventricular space. The free border is irregular or serrated, owing to uneven swelling of the individual cells. Death in ten hours. Hematoxylin and eosin; reduced from × 1,320.

they averaged from 12 microns, which we considered a high normal measurement, to 20 microns in height in advanced edema. In a few instances epithelial cells of gigantic proportions were found. These

21. Pettit and Girard (footnote 7, first reference).

22. Meek, W. J.: A Study of the Choroid Plexus, J. Comp. Neurol. **17**:286, 1907.

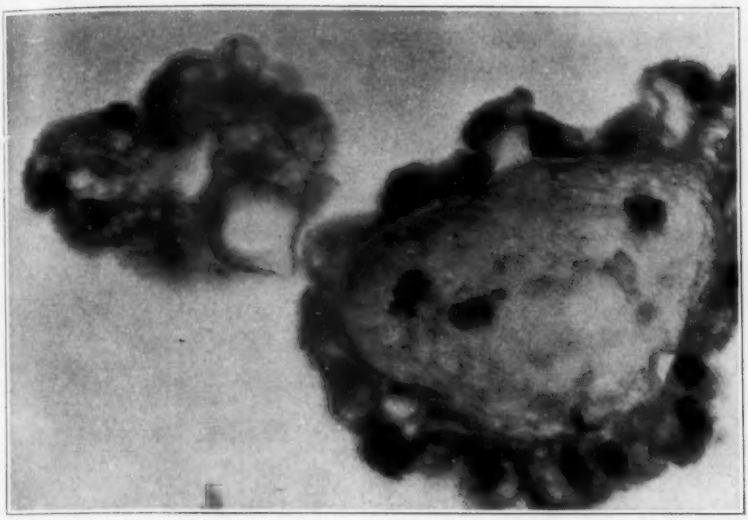

Fig. 4.—Vacuolization of choroidal epithelium in case 1. Unusually large vacuole about to rupture. A large vacuole adjacent to the basement membrane is also shown. Tremendous diffuse edema of the stroma is seen in the larger villus. Death in four hours. Hematoxlin and eosin; reduced from × 1,360.

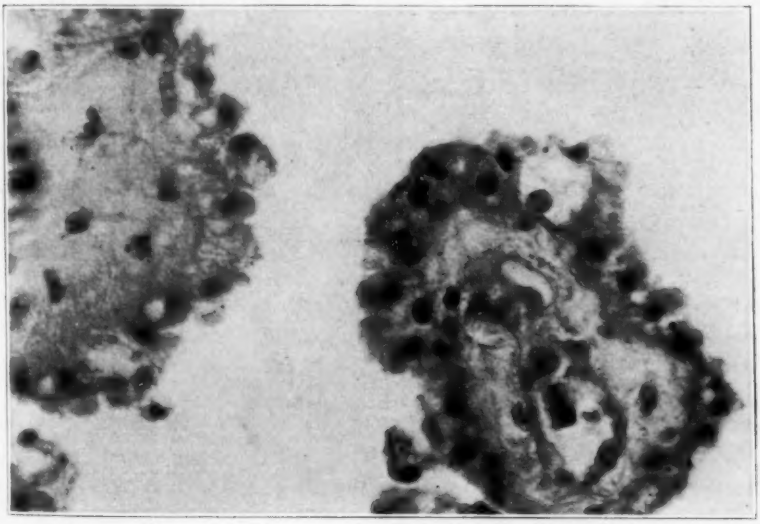

Fig. 5.—Vacuolization of choroidal epithelium in case 1. Very large vacuoles are found causing a disruption of the internal architecture of the cell. The irregularity of the basement membrane is evident. Marked generalized edema of the stroma in both villi is seen. Death in four hours. Hematoxylin and eosin; reduced from × 860.

measured from 26 to 27 microns in height, being easily two or three times as large as an epithelial cell of a normal choroid plexus. In many instances the measurement did not represent the true height of the cell, because the free margin was ragged and had undergone rupture and loss of substance. This could be seen many times when the process of secretion was rapid. This was particularly true when the individual cell was filled with numerous small vacuoles which seemed to have torn through its free margin. Findlay [6] has mentioned the presence of numerous small vacuoles which he believed on occasion coalesced to form larger ones.

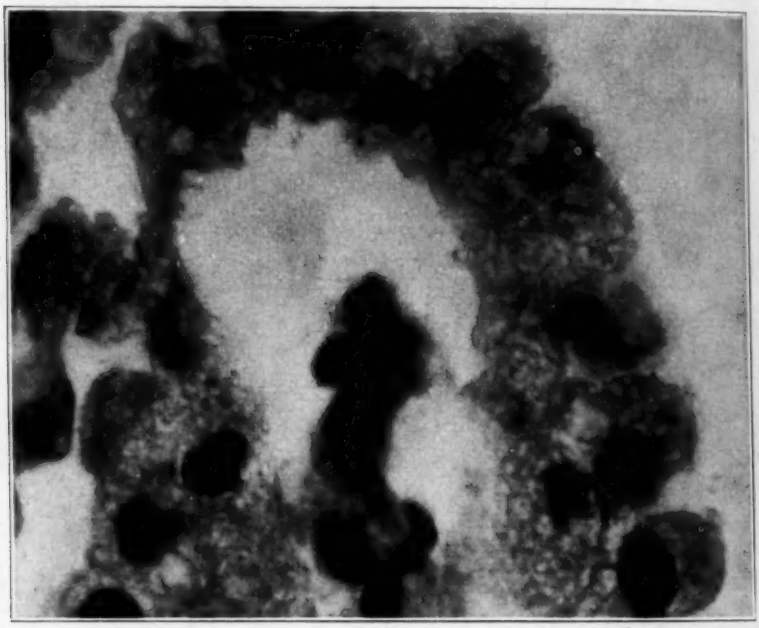

Fig. 6.—Vacuolization of choroidal epithelium in case 13. Epithelial cells loaded with minute vacuoles. A very narrow distal clear zone is seen. The connective tissue of the villus is compressed and the basement membrane is distorted by a collection of fluid. Death within three hours. Hematoxylin and eosin; reduced from × 2,960.

Vacuoles of two varieties have been found, either a single large one or numerous small ones. We have thought that the presence of a single vacuole represented a relatively slow process in the activity of the cell (fig. 4). In such cases the morphologic appearance of the cell seems to be fairly well preserved and there is little evidence of destruction of the cytoplasm or alteration of the nucleus. In some cases more than one of these large vacuoles coalesced to form a large, smooth-walled,

irregular space. Again, the cell was sometimes tremendously distended with a large irregular space occupying its center and suggesting in miniature the ragged walls of a cyst (fig. 5). In the majority of cases there was a predominance of numerous small vacuoles which appeared as minute rounded clear spaces in the cytoplasm of the cells (fig. 6). These were either spread evenly throughout the cell or predominated at its free margin. We have considered this type of vacuolization as representing a more rapid metabolic process. In such instances the cytoplasm was more broken up and the free cell margin presented a

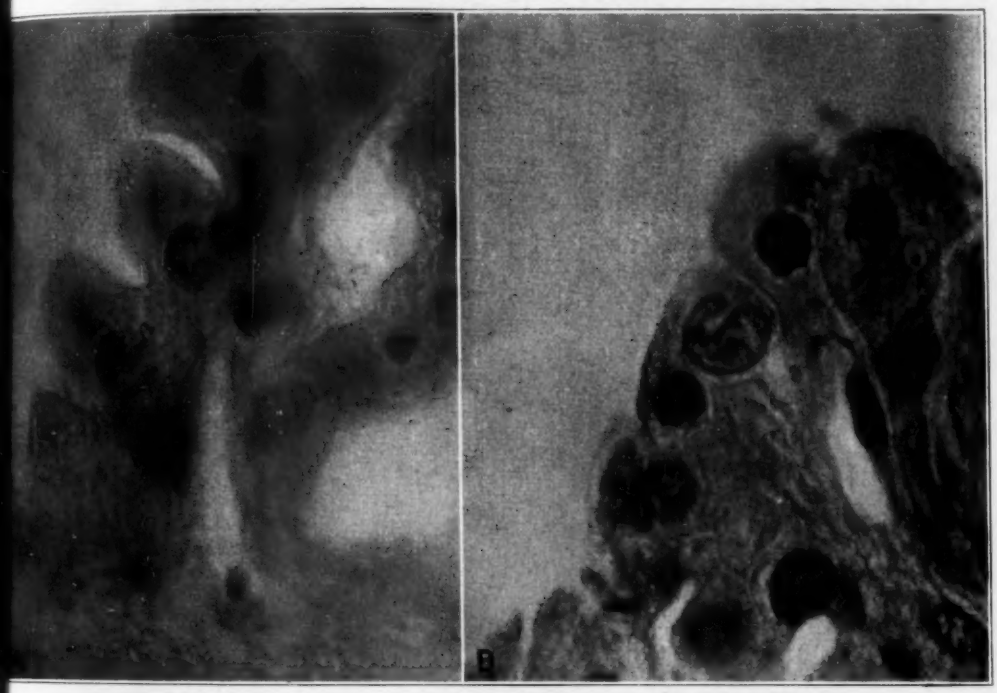

Fig. 7.—*A*, rupture of nuclear membrane, and *B*, horseshoe-shaped nucleus in case 24. Death two days after injury. Hematoxylin and eosin; reduced from × 1,800.

ragged appearance with bits of cytoplasm hanging in tatters in the ventricular space.

The nature of these vacuoles has given rise to much discussion. Do they represent active secretion of the cell? Most observers believe that they do. On the other hand, Becht [16] pointed out that they may represent absorption of fluid from the ventricle into the choroid plexus. He noted that actively secreting cells in certain other glands, such as the parotid, are smaller than quiescent ones, and consequently he did not

believe that an increase in the vacuolization and the size of the choroid epithelium necessarily indicates increased secretion. By analogy, he held that the cells should actually be smaller than normal during activity.

It has seemed to us that these vacuoles must be fluid containing both in the normal choroid and in the choroid following trauma. We do not believe that they are hyaline bodies or fat globules. When hyaline stains, such as van Gieson's stain, are used they still appear as clear spaces in the cell. Likewise we were unable to demonstrate the presence of fat in the vacuoles. With fat stains, such as Nile blue or

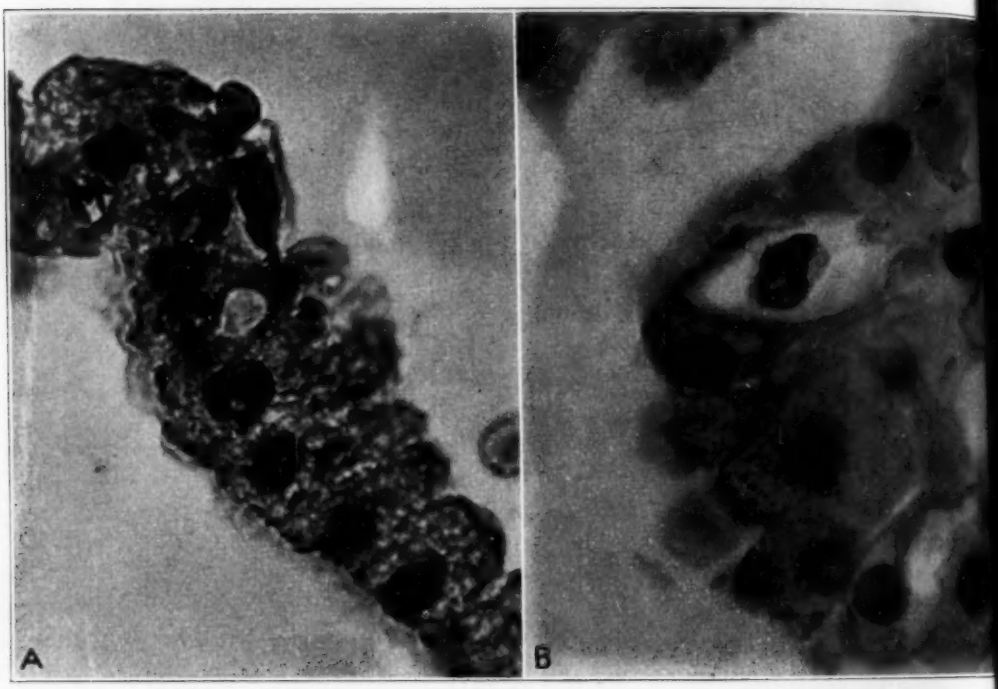

Fig. 8.—*A*, vacuolization of nuclei of epithelial cells in case 15. Death within three hours. *B*, nucleus enclosed in large vacuole in case 3. Death after ten hours. Hematoxylin and eosin; reduced from × 1,800.

scarlet red, Sundwall [23] also was unable to demonstrate fat in the choroid plexus of the ox.

Granulation of the cell cytoplasm was variable in amount, depending on the nature of the metabolic process. If this was slow the normal granular appearance of the cells was preserved. If there were a large number of minute vacuoles they gave an appearance of increased granu-

23. Sundwall, J.: The Choroid Plexus with Special Reference to Interstitial Granular Cells, Anat. Rec. **12**:221, 1917.

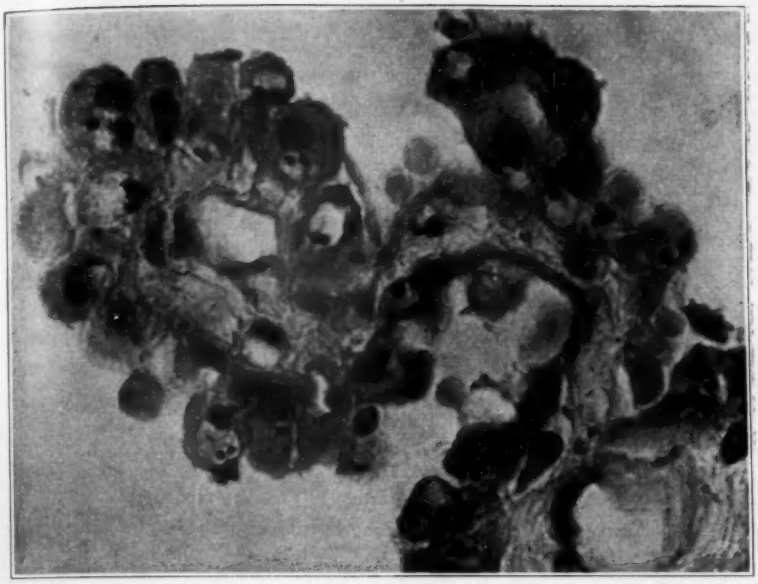

Fig. 9.—Pigmentation of choroidal epithelium in case 13. Practically all of the cells are vacuolated in this villus and most of them contain granular pigment. In one instance it is projecting into the ventricle. Death within three hours. Hematoxylin and eosin; reduced from × 1,400.

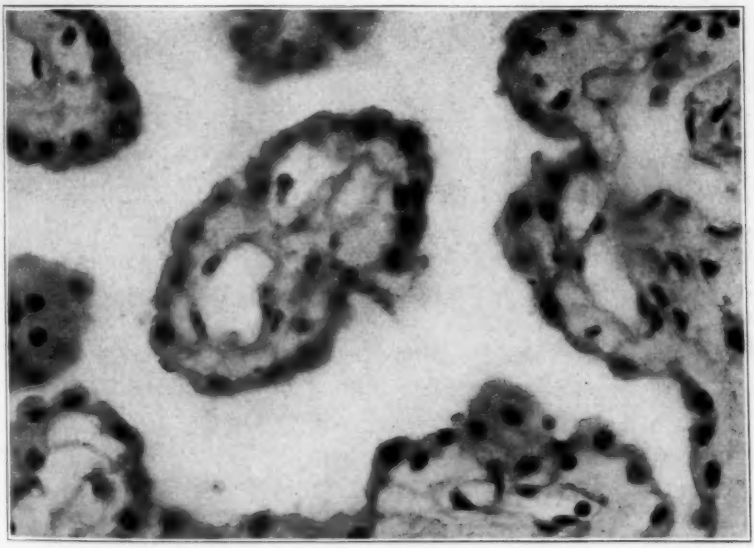

Fig. 10.—Collections of fluid in stroma in case 35. Local collections of fluid in the stroma which have distorted and compressed the basement membrane of the epithelial cells. Death within one hour. Hematoxylin and eosin; reduced from × 340.

lation of the cell. In reality, we believe, they represented increased vacuolization. When a group of cells was cut in cross-section they often seemed to be separated by irregular fluid spaces, the nature of which was not entirely clear.

Changes in the morphologic appearance of the nuclei of the choroid epithelium were often seen. Usually the nucleus was swollen moderately and at times markedly. Again vesiculation was present. When the nucleus was greatly swollen actual rupture of the membrane with scattering of the chromatin content into the adjacent cytoplasm was occasionally observed (fig. 7*A*). In other instances there was a shrinkage and distortion of the nucleus with the chromatin material

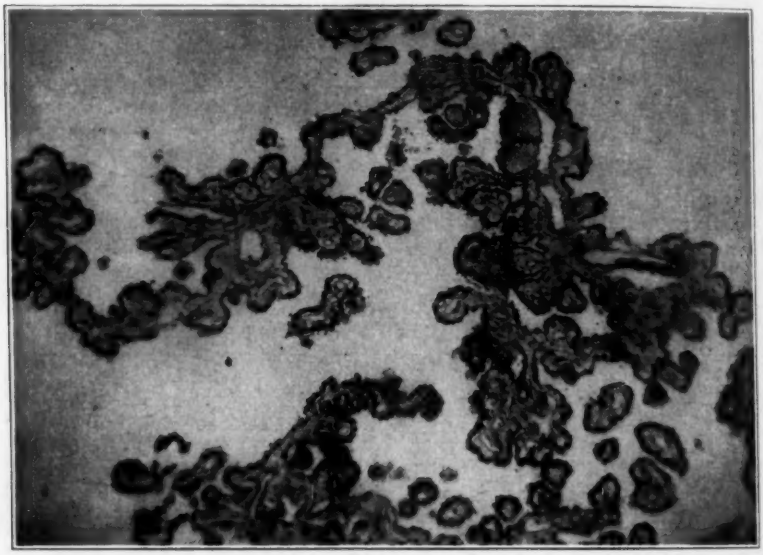

Fig. 11.—Moderate edema of stroma in case 3. Death ten hours after injury. This degree of edema is fairly characteristic of most of our cases. Hematoxylin and eosin; reduced from × 200.

condensed into an irregular shape, the particles being large and closely packed together. In other cases nuclear distortion took place without appreciable swelling or shrinkage of the structure. This characteristically took the form of a pseudopod suggesting the outline of a gourd. In some cases the handle was bent around so that the whole nucleus was horseshoe-shaped (fig. 7*B*). In some instances, especially where the process was rapid and associated with numerous small vacuoles in the cytoplasm of the cell, the nuclei also became vacuolated (fig. 8*A*). The vacuoles either were in the form of a single round or oval body, or were dumb-bell shaped. In some instances it was possible to see

invaginations into the nuclear membrane from an adjacent vacuole in the cytoplasm. This would suggest that it may be the method of vacuole formation as well as of nuclear distortion, although it does not explain all the pictures observed in the latter instance. Findlay [6] likewise described vacuolization of the nuclei of the choroid epithelium. At times we have seen the nucleus lying entirely external to the cell in the free ventricular space. A nucleus has also been observed lying entirely within a large vacuole (fig. 8*B*).

Pigmentation is present in a minor degree in the normal choroid plexus of man. In this series the pigment was often found to be increased, usually being present in vacuoles (fig. 9). It occurred in the shape of irregular stars or crystals with bizarre shapes and sharp or

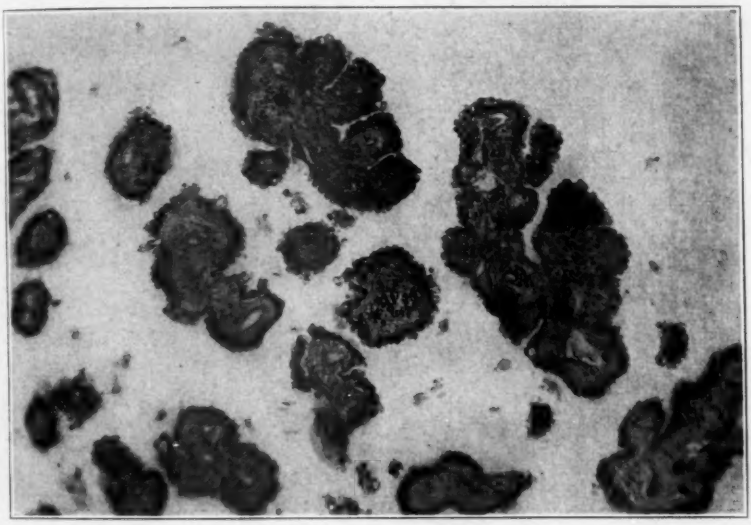

Fig. 12.—Extensive edema of stroma in case 1. This degree of edema was present in only four cases. It usually occurs from two to four hours after injury. Death within four hours. Hematoxylin and eosin; reduced from × 200.

irregular points. It was usually located in the periphery rather than the center of a vacuole. This might suggest that it did not float in the fluid, but sank to the most dependent portion. Flather,[24] in writing of the pigmentation found in animals, called it hemosiderin. In our cases iron was not shown by the potassium ferrocyanide test, although it was present in the fibrin masses both within and without the blood vessels. We have felt that the pigment was iron-free, possibly hematoidin. In

24. Flather, M. D.: A Study of the Haemosiderin Content of the Choroid Plexus, Am. J. Anat. **32**:125 (Sept.) 1923.

some instances the choroid epithelium was found to be broken up, and bits of pigment were seen in its margin or lying free in the ventricular cavity. Pigmentation was not confined to the choroid epithelium, but was also present in lesser amounts in the stroma of the plexus.

Normally the basement membrane is preserved intact. This was true in our series when the accumulation of fluid was moderate in degree and in the form of small globules. In such cases fluid spaces were usually present between the basement membrane and the wall of a blood vessel. When the process was more extensive and probably more rapid, the free fluid was found in large spaces in the stroma and the basement membrane was often torn. In certain instances it was greatly

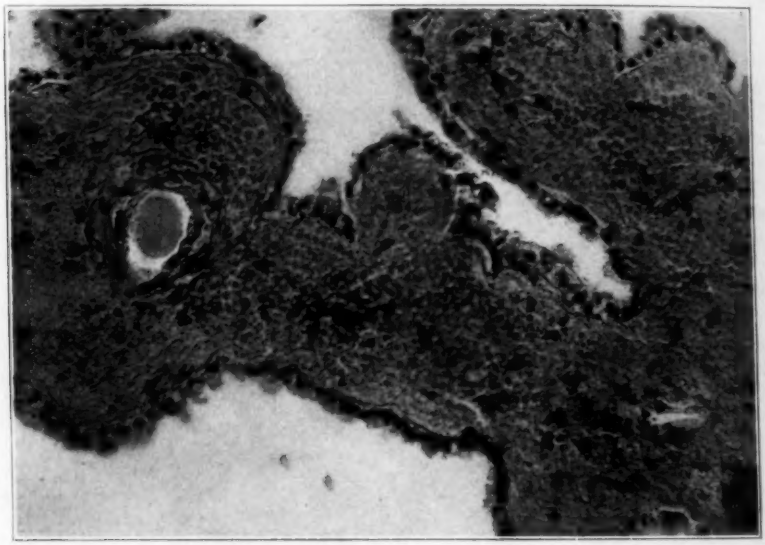

Fig. 13.—Hemorrhage into stroma in case 19. Extensive hemorrhage into edematous stroma. The red blood cells are well preserved. Diffuse pigmentation of the stroma and the choroidal epithelium. Death after ten hours. Hematoxylin and eosin; reduced from × 860.

distorted or even destroyed, so that the inferior aspects of the cells were extremely irregular and appeared as though fluid were pushing into or between them (fig. 10). In slower processes vacuoles were found which indented the basement membrane and pressed into the base of the cell. More characteristically the first indication of the passage of fluid through the cell was a flattened vacuole lying along the basement membrane or less commonly along the lateral cell wall. As the vacuole increased in size, it became more rounded and came in contact with the inferior aspect of the nucleus. The nucleus at times was indented by

the vacuole, much like the basement membrane described. These basilarly situated vacuoles suggest the canaliculi which Sundwall [23] found in the choroid plexus of the ox.[25]

The connective tissue of the stroma is inconspicuous in the normal choroid plexus. After injury various degrees of edema were observed. These were most striking under lower magnification. In some instances there was but minor separation of the fibrous constituents and only small collections of fluid were found in the stroma (fig. 11). In others the swelling was more diffuse and distention reached tremendous

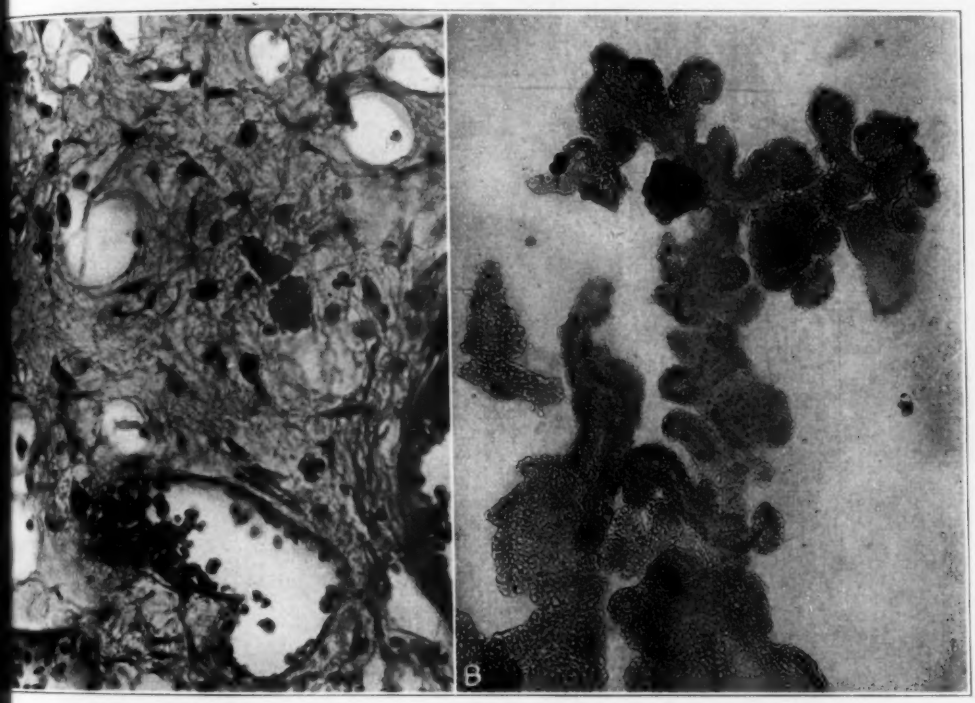

Fig. 14.—*A*, phagocytosis of pigment in stroma in case 22. Death in five days. Hematoxylin and eosin; reduced from × 560. *B*, pigment in choroid plexus in case 19. Death in ten hours. With the Prussian blue method, calcospheres stained deep blue and small pigment granules brown; reduced from × 95.

proportions (fig. 12). The fluid at times accumulated in large spaces in various portions in the stroma, but characteristically between the

25. The question arises whether Sundwall was describing normal or traumatic choroid plexuses, as the method of slaughtering oxen is usually by striking on the head with a sledge hammer. If this was the method of killing employed, the animal would certainly suffer a concussion and contusion of the brain and present pathologic changes in the choroid.

blood vessels and basement membrane. These collections of fluid at times took the form of numerous small droplets. When they became enlarged the smaller individual septums were broken down so that extensive spaces were found. From our observation in several cases showing early changes it would seem as though fluid may collect in the loose connective tissue of the stroma before it appears as vacuoles in the choroidal epithelium. Hemorrhage at times occurred in the stroma, often with the red blood cells well preserved (fig. 13).

Certain changes were found in the connective tissue cells. If the edema of the stroma was moderate the nucleus might be swollen so that

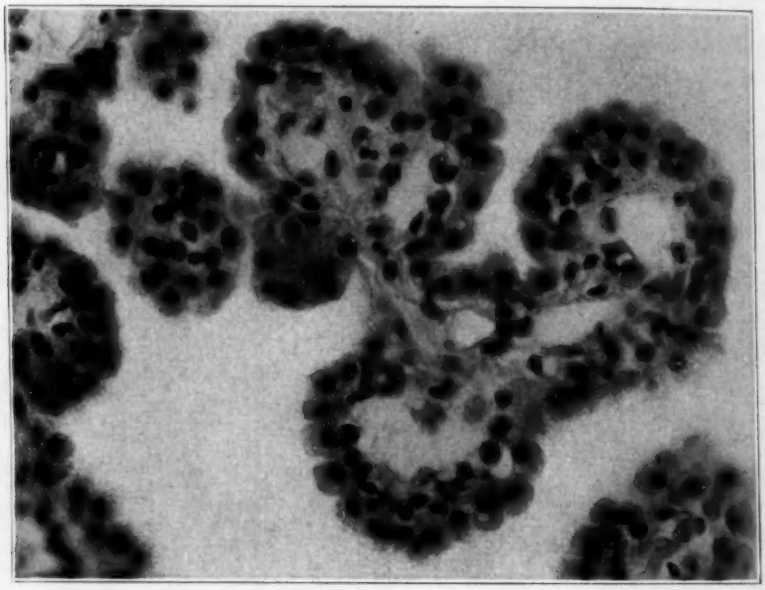

Fig. 15.—Wandering cells in stroma in case 41. The edematous stroma contains many leukocytes. There was no gross evidence of meningitis in this case Death in three and a half days. Hematoxylin and eosin; reduced from × 450.

it appeared vesicular or more rounded than normal. It was normally oval and much elongated. In other cases the nuclei took peculiar shapes with indentations and projecting pseudopodia. The cells and nuclei were occasionally vacuolated. If the nuclei became vesicular the chromatin assumed a circular arrangement as in plasma cells. Pigmentation was often present in the stroma, in which case the pigment granules were contained in phagocytic cells or sometimes appeared even in the leukocytes (fig 14*A*). Noniron-containing pigment was demonstrated by the specific potassium ferrocyanide test (fig. 14*B*). Findlay [6] likewise described pigment as being present in phagocytic

cells of the stroma, as well as within vacuoles of the choroid epithelium. Masses of "fibrin," referred to by us as "fibrin thrombi," were sometimes found outside as well as inside the lumen of the vessels.[26] These took a deep bluish purple with the routine stains. With the iron stains, i. e., potassium ferrocyanide, they were found to contain much iron in their meshes. In some cases these "fibrin thrombi" were numerous and formed a conspicuous feature in the low power magnifications. They were usually found to be more numerous in older persons. Osnato and Giliberti [27] mentioned the occurrence of these "fibrin thrombi" and concluded that their presence is due to a disturbance of the colloidal equilibrium of blood calcium, favoring its precipitation. Psammoma bodies

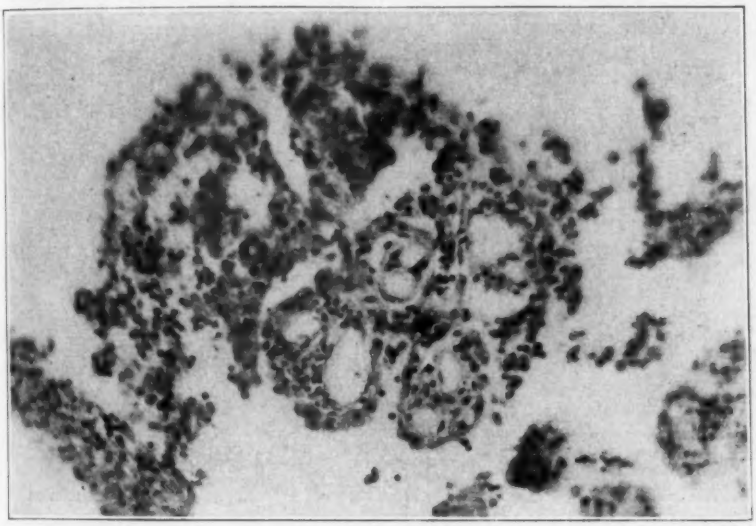

Fig. 16.—Wandering cells in stroma and ventricles in case 40. Extensive infiltration of leukocytes in choroid plexus in a clinical case of meningitis following injury. Death in nineteen days. Hematoxylin and eosin; reduced from × 200.

were also frequent in the pedicle of the choroid plexus and likewise increased in number as age advanced. The blood vessels were usually distended, owing largely to preliminary embalming. This also explained

26. Because these structures are found in normal as well as in abnormal choroid plexuses, their presence is not indicative of previous trauma. It is evident from their situation and incidence, as well as from their staining reaction, that they are closely related to the psammoma bodies that occur in the pedicle of the plexus.

27. Osnato, M., and Giliberti, V.: Postconcussion Neuroses; Traumatic Encephalitis: A Conception of Postconcussion Phenomena, Arch. Neurol. & Psychiat. **18**:181 (Aug.) 1927.

the fact that most of them were empty, as the blood had been washed out by this process. At times the nuclei of the endothelial cells of the vessels were swollen and vesicular. This was considered as secondary to edematous and hyperemic changes in the choroid plexus.

In many cases round or polymorphonuclear leukocytes were seen in the stroma of the choroid plexus (fig. 15). They were often present microscopically, even when meningitis was not observed grossly or present clinically. They were, of course, always found in greater numbers when meningitis was present clinically (fig. 16).

The normal ependyma (fig. 17) consists of a single layer of epithelial cells of the squamous or cuboidal type, attached to the underlying substance of the brain by a delicate basement membrane. However, as the choroid plexus is approached these cells become more columnar.

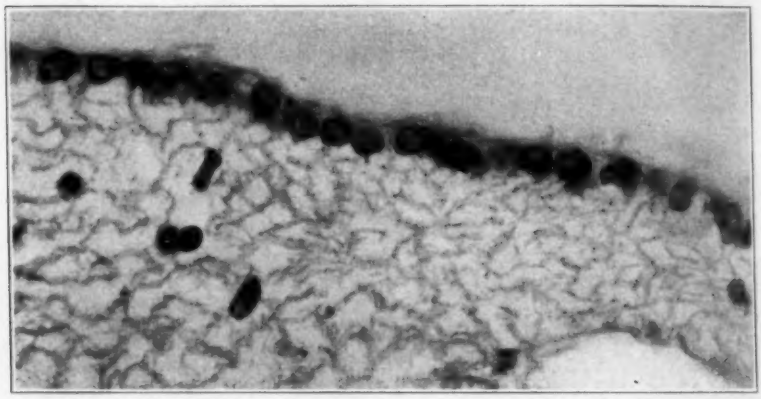

Fig. 17.—Normal ependyma. Cells are cuboidal, having an indistinct basement membrane. A few small vacuoles can be seen between the nuclei in several cells. They are normally present in small numbers in the ependyma. Hematoxylin and eosin; reduced from × 1,400.

The low normal or squamous type has been found to measure approximately 5 microns in height. The cuboidal type varies from 6 to 9 microns in height, and the columnar type averages from 11 to 13 microns. Normally they may contain a few vacuoles. Their nuclei are oval and occupy a position near the base of the cell with the long diameter corresponding to that of the cell. A thin indefinite basement membrane can be made out in places. This in part may be composed of the basal lining of the cells themselves. The subependymal tissue usually shows little edema and does not tend to distort the alinement of the basement membrane.

Following injury we found changes in the ependyma in many respects closely resembling those seen in the choroid plexus. The

epithelial cells were swollen in proportion to the edema present. Often they were from two to three times as high as a normal cell, some individual cells measuring as much as from 30.1 to 30.25 microns. The nuclei were often pushed to a distal position in the cells by the underlying wall of advancing fluid, so that they gave a palisaded appearance (fig. 18). The fluid often formed a line of vacuoles behind them. Again they were pushed about in an eccentric manner by the vacuoles in the ependymal cells. These vacuoles at times literally tore the cells to pieces and little was left except the tattered margin and the displaced nucleus. It is possible that the whole cell, including the basement membrane, was pushed far forward in some instances. The basement mem-

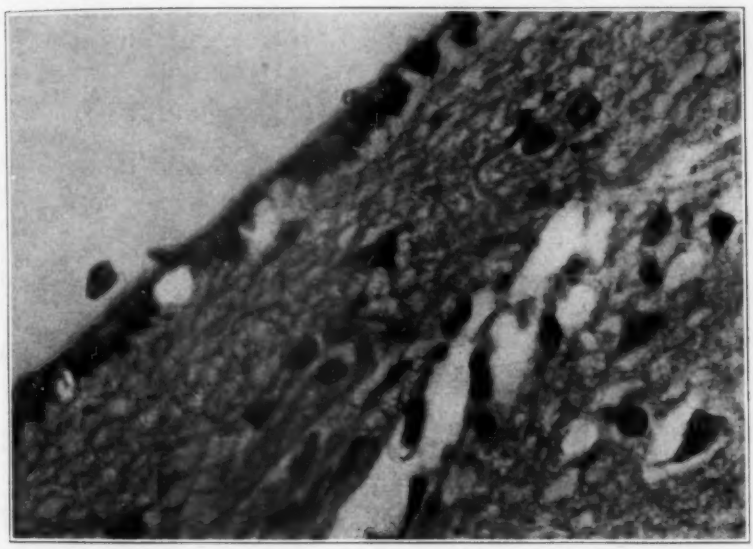

Fig. 18.—Moderate vacuolization of ependymal epithelium in case 11. Most of the fluid is in the base of the cells, apparently pushing the nuclei forward and giving a palisaded appearance. Death in twenty hours. Hematoxylin and eosin; reduced from × 1,400.

brane was usually distorted and was often broken or entirely destroyed by the fluid pressure from below. The subependymal tissue likewise showed varying degrees of fluid distention. In minor or moderate cases it was but little changed, with perhaps some increase in the size of the interstitial spaces. In "full blown" edema, however, the intercommunicating septums were entirely torn apart so that great lakes of fluid often could be seen piling up behind the ependymal lining (fig. 19). On occasion the ependymal cells were separated so that fluid could be seen passing between them. In cases of bleeding into the ventricle, a layer of

broken-down red blood cells in various degrees of degeneration could be seen clinging to the free margin of the ependymal lining (fig. 20).

INTERPRETATION OF OBSERVATIONS

In reviewing this series of cases, it seems to us that the increased vacuolization, both of the epithelium of the choroid plexuses and of the ependyma, suggests that these structures are capable of secretion of fluid. If this is true it is further evidence that the choroid plexuses in particular are the chief sources of cerebrospinal fluid. It seems logical to conclude that following severe injuries to the head, the activity of the choroid plexuses as well as of the ependyma is stimulated. This

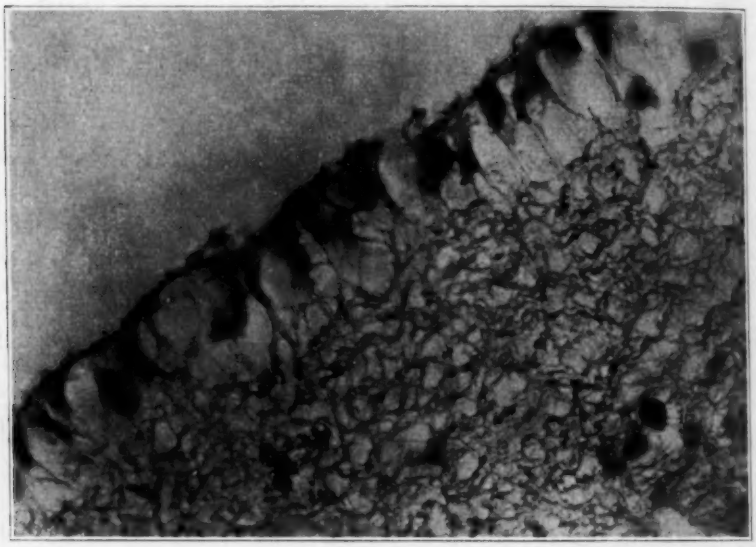

Fig. 19.—Marked vacuolization of the "full blown" ependyma in case 24. The cells are markedly distorted by the large vacuoles. One of them appears to have broken through into the ventricles. The subependymal tissue appears to be definitely edematous. Death two days after injury. Hematoxylin and eosin; reduced from × 1,400.

probably accounts for the excess of cerebrospinal fluid found clinically in such cases. This process apparently starts immediately following an injury and proceeds with varying intensity until the death of the patient or until his recovery begins. On occasion it is undoubtedly influenced by other concomitant factors, such as alcoholism, meningitis, ventricular hemorrhage, decompressive operations or the employment of hypertonic solutions in treatment. From an experimental standpoint the intravenous use of hypertonic solutions apparently retards the activity of the gland while the administration of hypotonic solutions, as shown by

Weed [28] and Ferraro,[29] stimulates it. In Ferraro's series of rabbits, in which hypotonic solutions were introduced intravenously, the vacuolization of the choroid plexus was greatly increased. Edema of the stroma was also present. In his animals there were large collections of fluid in the ependymal cells as well as an increase in the vacuolization of the subependymal tissues. His observations were practically identical with, although more extensive than, those made in this series. This is to be expected, as it is possible to produce more marked edematous changes in the "water brain" of the rabbit than would reasonably follow trauma in man. In our series of cases in which intravenous injections of hypertonic dextrose solution were given, the changes in the choroid plexus

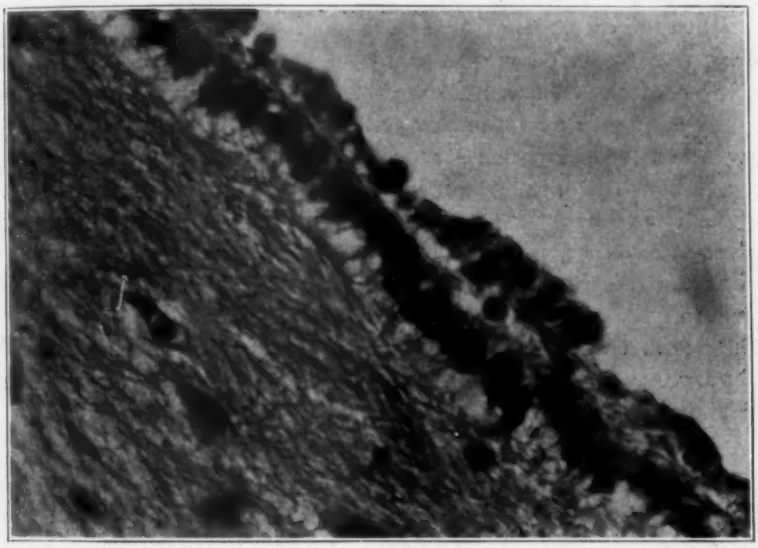

Fig. 20.—Vacuolization of ependymal cells and ventricular hemorrhage in case 10. Vacuolization of ependyma is moderately increased, the fluid vesicles displacing and distorting the nuclei. Red blood cells in various stages of degeneration are found along its free margin. Grossly the ventricles were filled with blood. Death within twenty minutes. Hematoxylin and eosin; reduced from × 1,400.

and the ependyma were less marked than otherwise. The greatest degree of change was found in the patients who died from two to four hours after injury to the head. Practically none of these patients received hypertonic dextrose solution. It would be interesting to

28. Weed, L. H.: The Effects of Hypotonic Solutions upon the Cell-Morphology of the Chorioid Plexuses and Central Nervous System, Am. J. Anat. **32**:253 (Sept.) 1923.

29. Ferraro, A.: The Reaction of the Brain Tissue to Intravenous Injection of Hypotonic Solutions, J. Nerv. & Ment. Dis. **71**:129 (Feb.) 1930.

speculate as to what extent changes may occur in the choroid plexuses and ependyma in nonfatal cases.

In attempting to interpret our observations, the normal physiologic process of the choroid plexus is a constantly recurring question. Whether the cerebrospinal fluid is formed by a process of secretion, excretion or dialyzation has not been answered. If it is a secretion, as we have come to believe, two mechanisms for the formation of this fluid may be considered. Is it a result of selective activity of the choroidal epithelium or is it a vasomotor phenomenon? Findlay [6] and Mott [30] both described nerve fibers in the choroid plexuses of the calf, sheep and man. These are in the neighborhood of the blood vessels of the stroma and take a plexiform arrangement. They were not able to demonstrate terminal fibrils to the epithelial cells themselves. From a histologic standpoint it seems that the blood vessels of the choroid are equipped with a vasomotor control. Whether the secretion of cerebrospinal fluid depends wholly or in part on vasomotor activity is an unsettled question. However, the presence of such nervous elements suggests a function of some sort, although as yet this function is unknown. It may be that increased production of fluid by the administration of vasodilators, such as pilocarpine and ether, may result from an increase in blood flow to the plexuses. It is further possible that the increase in fluid production following injury to the head may be due to a paralytic action on the vasoconstrictors either directly or perhaps indirectly through a secondary substance, as has been suggested in the production of local edema of peripheral soft tissues after injury.

CONCLUSIONS

1. Increased vacuolization of the choroidal epithelium together with heightening of the individual cells is usually found following fatal injury to the head. This may occur in the form of single large circumscribed vacuoles or as numerous small droplets giving the impression of cellular edema. These changes vary within wide limits, and, beginning immediately, apparently reach their maximum in from two to four hours following injury. Other factors, such as shock, the time interval between injury and death and the use of hypertonic dextrose solution, undoubtedly influence the ultimate picture. By analogy, it may be assumed that similar changes occur in nonfatal cases.

2. A variable degree of edema of the stroma takes place under these circumstances. It is felt that this edema probably precedes the changes in the epithelial cells. On occasion, hemorrhagic extravasations are

30. Mott, F. W.: The Pathology of the Cerebro-Spinal Fluid, Lancet **2**:1 and 79, 1910.

observed, but more frequently one sees pigment in the stroma and epithelial vacuoles, which may indicate disintegration of red blood cells. We believe that this pigment is hematoidin.

3. Subependymal edema, as well as an increase in the vacuolization and the height of the ependymal cells, often occurs. These changes are variable in degree and are not as constant as those found in the choroid plexus.

4. The changes are similar to those found in the "water brain" of animals produced experimentally by the intravenous injection of hypotonic solutions.

5. Whether the changes observed are due to selective activity of the epithelial cells or are secondary to vasomotor phenomena is as yet undetermined.

THE SIGNIFICANCE OF FAT EMBOLISM*

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INTRODUCTION

Fat embolism is that condition which occurs when a liquid oil enters the circulating blood and is transported in globules large enough to obstruct the lumen of blood vessels in different parts of the body. It has been described frequently as an important complication of trauma in human beings, and occasionally may be severe enough to be a definite cause of death. Two well defined clinical and pathologic varieties of fat embolism are now recognized: (1) the pulmonary form, in which the emboli obstruct the smaller blood vessels of the lungs and produce symptoms of asphyxia, and (2) the cerebral form, in which the emboli gain entrance to the arterial circulation, block the arterioles in the different organs, especially the brain, and produce symptoms referable to the central nervous system.

Fat embolism of a less serious nature has been found at necropsy not only in persons who have suffered from trauma, but in others who do not give a traumatic history. At the present time, while it is recognized that the condition is a definite result of injury, many believe that it can occur from other causes.

I have made an attempt to discover how far this belief is correct. The literature on fat embolism is reviewed briefly, and a number of routine necropsies of the Office of the Chief Medical Examiner of New York are studied for the purpose of ascertaining the incidence and importance of this condition.

The subject has been subdivided for convenience into the following parts:

Fat Embolism in Human Pathology: Etiology.
Fat Embolism in Human Pathology: Clinical Signs and Pathologic Lesions:
(*a*) Pulmonary Fat Embolism.
(*b*) Systemic or Cerebral Fat Embolism
(*c*) Diagnosis and Treatment of Fat Embolism.
Fat Embolism in Animal Experiments.
Comment and Summary.

FAT EMBOLISM IN HUMAN PATHOLOGY; ETIOLOGY

In the literature, two main classes of conditions are associated with fat embolism. The first category includes true etiologic factors, such

* Submitted for publication, Oct. 20, 1930.
* From the office of the Chief Medical Examiner of New York.

as traumas to the adipose tissues of the body and the intravenous injection of oily substances. The second category comprises a variety of processes which have been mentioned as causative agents but which have a doubtful significance in this respect.

The true etiologic factors are classified as follows:

Traumas to the adipose tissue:

1. Trauma to the osseous system
   (*a*) Fractures of the bones
   (*b*) Jarring of the skeleton
   (*c*) Orthopedic operations
2. Trauma to subcutaneous and intermuscular fat
3. Trauma to fatty viscera

Intravenous injection of various oils

The dubious etiologic factors are:

1. Burns
2. Postmortem processes
3. Poisons
4. Natural causes of death

TRAUMAS TO ADIPOSE TISSUE

Fat embolism is produced by physical injury to fatty tissue only when the three conditions enumerated by Gauss [1] are present: 1. The force must so injure the envelop of the fat cell that liquid fat is set free. 2. The force must tear small veins in the vicinity of the liquid fat. 3. Some mechanism must be present which will drive the liquid fat into the open ends of the torn veins and so introduce it into the general venous circulation. These factors operate in all cases of fat embolism due to trauma, but are especially applicable when the skeletal bone marrow is involved.

1. *Trauma to the Osseous System.*—A consideration of the structure of the long bones and the fatty bone marrow is necessary for a proper understanding of the close connection of skeletal injuries and fat embolism.

In normal infancy and childhood the long bones are easily bent and contain a red cellular marrow throughout. According to Landois [2] the fat present is composed of the less fluid oils, such as palmitin and stearin, with a smaller proportion of the more fluid olein. The architecture of the bone is more homogeneous, and the transition from the

1. Gauss, Harry: The Pathology of Fat Embolism, Arch. Surg. **9**:592 (Nov.) 1924.

2. Landois: Deutsche med. Wchnschr. **52**:283 (Feb. 12) 1926.

dense bone of the shaft to the cancellous bone of the extremities is more gradual than in adult skeletons.

By the usual process of growth, the cellular bone marrow becomes more and more fatty and the proportion of olein increases so that the oil is quite fluid at body temperature. The shaft and epiphyses are more clearly separated in structure, as the latter are composed of spongy cancellous bone filled with fatty marrow, while the shaft is a hard tube of dense bone, surrounding a friable vascular fatty marrow. All these anatomic peculiarities are important factors in the causation of fat embolism.

(*a*) Fractures of the Shafts of the Long Bones: The most frequent cause of fat embolism is fracture of the shaft of a long bone, especially in the lower extremity. Numerous reports have testified abundantly to this lesion as an important etiologic factor from the time of Busch,[3] in 1865, to the present day.

There are good reasons why fat embolism should accompany this type of injury. In the first place, many fat cells are ruptured and an appreciable amount of liquid oil is set free around the ends of the broken bones. As Gauss [1] pointed out, many veins are torn across, especially those in the haversian canals which are enclosed in a rigid tube of bone and cannot readily collapse. According to Bergemann,[4] the natural aspirating force of the veins will remove such liquid fat as may be set free and transport it to the main venous circulation and hence to the lungs. Any increase of internal tension in the area of injury, such as might occur from a marked hemorrhage or reflex spasm of the muscles of the extremity, will only increase the absorption of fat and, as a result, the severity of the embolism. The experiences of Siegmund,[5] Sutton [6] and others have established these facts beyond dispute.

According to Landois,[2] most of the serious cases of fat embolism after fracture occur in men between the ages of 20 and 50. Not only are these the years during which trauma is most likely to occur, but they are also the period when the bone marrow is especially fatty and contains the highest percentage of olein. As this oil is quite fluid at body temperature, it is more easily absorbed than the more viscous fats, palmitin and stearin, which are present in the fat in normal children. It is probably for this reason that a serious grade of fat embolism does not complicate fractures in children to the same degree as in adults.

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3. Busch, F.: Virchows Arch. f. path. Anat. **35**:321, 1866.
4. Bergemann, E.: Berl. klin. Wchnschr. **47**:1112 (June 13) 1910.
5. Siegmund, H.: München. med. Wchnschr. **65**:1076 (Sept. 24) 1918.
6. Sutton, George E.: Brit. M. J. **2**:368 (Oct. 15) 1918.

(*b*) Concussion or Jarring of the Skeleton: A few instances of severe fat embolism have been described in which the skeleton was subjected to a severe jarring without, however, fracture of the bones. In the case of Ziemke,[7] the casualty suffered was a fall from a height; a fall on an amputation stump was described by Beitzke;[8] a heavy blow on the right knee occurred in the case of Busse;[9] the patient of Ribbert[10] suffered an unknown injury of which the only trace was a small bruise on the right hip; and in the case of Frauendorfer[11] the patient fell into a pool at the moment an underwater bomb was exploded.

Except in the case of Frauendorfer, lesions of the bones and bone marrow were not described. This investigator noted a large number of lentil and pea-sized hemorrhages scattered through the fatty bone marrow, which he regarded as the result of the violence inflicted on the skeleton by the explosion. He also believed them to be the source of the fat emboli.

Schultze[12] offered a plausible explanation of the mechanism by which such hemorrhages are produced. The sudden jarring separates small portions of the flaccid fatty marrow from the firm bony cortex, ruptures a few fat cells and tears a few arteries and veins in the affected area. Numerous small hemorrhages then occur and raise the pressure inside the bony cavity, thus forcing liquid fat into the torn veins and so into the circulation.

(*c*) Orthopedic Operations: Various operations on bones and joints for the correction of deformities and other morbid conditions have frequently caused a fat embolism with fatal results. In a few instances the condition was due to open operations, as in Lucke's[13] case of resection of the hip joint, Vogt's[14] case of resection of the knee joint and Kirschner's[15] case of osteotomy. The bloodless correction of old joint contractures, especially about the knee, was made responsible for the same complication in the reports of Colley,[16] Lymphius,[17] Eberth,[18] Payr,[19] Clarke[20] and others.

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8. Beitzke: Centralbl. f. allg. Path. u. path. Anat. **24**:824 (Sept. 30) 1913.
9. Busse: Cor.-Bl. f. schweiz. Aerzte **43**:154 (Feb. 1) 1913.
10. Ribbert, Hugo: Cor.-Bl. f. schweiz. Aerzte **24**:457 (Aug. 1) 1894; Deutsche med. Wchnschr. **26**:419 (June 28) 1900.
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12. Schultze, Ernst O. P.: Arch. f. klin. Chir. **111**:573, 1918-1919.
13. Lucke: Centralbl. f. Chir. **6**:719 (Nov. 1) 1879.
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15. Kirschner, M.: Centralbl. f. Chir. **51**:465 (March 15) 1924.
16. Colley, Fritz: Deutsche Ztschr. f. Chir. **36**:322, 1893.
17. Lymphius, M.: Centralbl. f. Chir. **23**:800 (Aug. 15) 1896.
18. Eberth, J. C.: Fortschr. d. Med. **16**:251 (April 1) 1898.
19. Payr, E.: München. med. Wchnschr. **45**:885 (July 12) 1898.
20. Clarke, B. Earl: Fat Embolism, J. A. M. A. **88**:919 (March 19) 1927.

In short, fat embolism is accepted as a possible serious complication of orthopedic operations and is considered by many as referable, not only to the necessary trauma of the operation, but also to the abnormal conditions of the bones and bone marrow of the patients. Generally the skeletal deformities lead to prolonged rest in bed and disuse of the extremities, with the result that the marrow soon becomes fatty and the bone soft and osteoporotic. The manipulations during the operation cause considerable distortion of the bone, a general rise of intra-osseous pressure and rupture of fat cells and veins. Conditions are thus favorable for the introduction of fat into the circulation. In a few instances injuries of the soft parts, muscular tears, epiphyseal separations and actual fractures serve to increase the intensity of the embolism.

2. *Trauma to the Adipose Tissue of the Skin and Intermuscular Areas.*—Injuries that rupture the subcutaneous and intermuscular fat cells not infrequently cause a fat embolism of a severe grade, as the same mechanisms operate just as they do in the case of skeletal injuries. Cases of this sort were described by Flournoy,[21] Pinner [22] and Buerger.[23]

The case of Buerger [23] was a good example of injury to the subcutaneous fat, in which a fat embolism is especially likely to develop. A woman, aged 72, was beaten with a club, and suffered extensive separation of the dermis from the muscular fascia. The subcutaneous fat was torn, forming large pockets full of blood and oil. No fractures were noted. At necropsy, the lungs contained a large number of fat emboli.

Injuries to the pelvic fatty tissue by the passage of the fetal head through the birth canal are said to cause fat embolism. Cases of this sort were reported by Warthin [24] and Virchow.[25]

Operative incisions in the subcutaneous fat of obese persons were mentioned as a cause of fat embolism by Ferguson [26] and by Bissel.[27]

3. *Trauma to the Fatty Viscera.*—In rare instances a fatty internal organ, such as the liver, may be ruptured and death may result not from shock or hemorrhage but from an extensive fat embolism. Cases of this kind were described by Hamilton [28] and Engel.[29] The latter

21. Flournoy: Centralbl. f. Chir. **5**:703 (Oct. 19) 1878.
22. Pinner, O.: Berl. klin. Wchnschr. **20**:185 (March 26) 1883.
23. Buerger: Vrtljschr. f. gerichtl. Med. **39**:159, 1910.
24. Warthin, Aldred Scott: Internat. Clin. **4**:171, 1913.
25. Virchow, R.: Berl. klin. Wchnschr. **23**:489 (July 26) 1886.
26. Ferguson, H. F.: Brit. M. J. **1**:584 (March 16) 1895.
27. Bissel, Wayne W.: Surg. Gynec. Obst. **25**:8 (July) 1917.
28. Hamilton, D. J.: Brit. M. J. **2**:474 (Oct. 6) 1877.
29. Engel, H.: München. med. Wchnschr. **48**:1046 (June 25) 1901.

suggested that the embolism was caused by compression which forced fat from the liver cells into the torn ends of the small venules of the liver.

Siegmund [5] noted that fat embolism is occasionally associated with bullet wounds of the head which tear the brain tissue extensively. In these cases, however, the grade of the embolic process is usually slight.

INTRAVENOUS INJECTION OF VARIOUS OILS

The injection of oil intravenously will produce fat embolism, a fact that has been demonstrated repeatedly by experiments on animals. It is only rarely, however, that this is duplicated in human beings. According to Weingarten,[30] the hypodermic injection of oily substances therapeutically can produce a slight grade of fat embolism. Koch [31] injected liquid human fat into a scar of the neck and elicited symptoms that suggested that a nonfatal grade of fat embolism had been produced. Fibiger [32] described a case in a man who received 50 cc. of olive oil intravenously and who died as a result of the injection. Such examples of the condition, however, are exceptional as far as human pathology is concerned.

MORBID PROCESSES ASSOCIATED WITH FAT EMBOLISM: DUBIOUS ETIOLOGIC FACTORS

Fat embolism has been described in connection with a variety of conditions with which, however, the etiologic relationship is not altogether obvious.

Burns.—Several investigators have found fat emboli in the pulmonary vessels of bodies that have been burned, and much controversy exists regarding the significance of this association. Olbrycht [33] claimed that fat embolism is caused solely by antemortem burns and only when the burning is more severe than the first degree. According to him, the heat renders the fat fluid and opens the smaller vessels so that it can gain entrance to the circulation. Others, including Groendahl,[34] Weimann [35] and Harbitz,[36] are inclined to question this interpretation, and to attribute the fat emboli to associated injuries. Groendahl pointed out that the degree of fat embolism described in cases of burn is usually slight and of minor importance.

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30. Weingarten, R.: Schweiz. med. Wchnschr. **7**:248 (March 20) 1926.
31. Koch, Herman: Deutsche Ztschr. f. Chir. **186**:273, 1924.
32. Fibiger, quoted by Groendahl: Deutsche Ztschr. f. Chir. **111**:56, 1911; and by Wegelin: Schweiz. med. Wchnschr. **4**:133 (Feb. 8) 1923.
33. Olbrycht, J.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **1**:642, 1922.
34. Groendahl, Nils Backer: Deutsche Ztschr. f. Chir. **111**:56, 1911.
35. Weimann, W.: Virchows Arch. f. path. Anat. **264**:1, 1927.
36. Harbitz, Francis: Vrtljschr. f. gerichtl. Med. **45**:34, 1913.

Harbitz, however, mentioned that masses of liquid fat were found in the larger systemic veins of the trunk but not in the lungs in bodies that had been thoroughly cooked by flame. He expressed the belief that the process was caused entirely by the postmortem action of the heat which contracts the skin surface, liquefies the fat and forces it onward into the vessels.

Postmortem Processes.—According to Westenhoeffer,[37] a condition simulating fat embolism has been produced by the action of a postmortem gas bacillus decomposition in the marrow cavity of the shaft of the long bones. In a woman who died as the result of a septic abortion, necropsy showed numerous fat globules in the pulmonary vessels. The long bones showed marked invasion by gas bacilli, which Westenhoeffer attributed to the fact that the marrow in this case was rich in cells and so was a good nutrient medium for the organism. The formation of gas increased the intra-osseous pressure, freed the fat from the cell envelop and forced it through the veins into the pulmonary vessels.

Neureiter and Strassman[38] pointed out that the fat emboli in Westenhoeffer's case could have been due to some antemortem process, but they believed that postmortem transportation of fat by gaseous decomposition is possible. Buerger,[23] on the other hand, regarded fat embolism as an intravital phenomenon in every case and declared a postmortem etiology unthinkable.

In any event, the degree of postmortem embolism is comparatively slight, and the validity of Westenhoeffer's theory has not been fully proved.

Poisons.—Fat embolism has been cited in connection with death from various poisons. Groendahl[34] mentioned poisoning by phosphorus, potassium chlorate, potassium bichromate, potassium cyanide, corrosive mercuric chloride, U. S. P., phenol and alcohol as the alleged causative factor, but he questioned any etiologic relationship between the poisoning and the embolism.

Puppe[39] described fat globules in the vessels of a person who died of subacute phosphorus poisoning. He believed that they were caused by fatty degeneration of normal white blood cells which coalesced inside the vessel and formed fat emboli.

MacMahon and Weiss[40] reported a fatal case of poisoning by carbon tetrachloride associated with a marked fatty degeneration of

37. Westenhoeffer, M.: Virchows Arch. f. path. Anat. **170**:517 and 528, 1902; Vrtljschr. f. gerichtl. Med., 1904, supp., p. 184.

38. Neureiter, F., and Strassman, G.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **1**:204, 1922.

39. Puppe: Vrtljschr. f. gerichtl. Med., 1896, supp., p. 94.

40. MacMahon, H. E., and Weiss, S.: Am. J. Path. **5**:623 (Nov.) 1929.

the liver and with a macroscopic demonstration of fat in the blood of the pulmonary artery. On microscopic examination, however, fat emboli were not found in the finer blood vessels of the lung, and a diagnosis of fat embolism was not made.

Winogradow [41] discovered fat emboli in a case of poisoning by potassium chlorate and believed them to be due to multiple hemorrhages in the fatty bone marrow caused by the toxic action of the chemical.

Burns and Bromberg [42] described a case of fat embolism in an obese colored woman who had received an injection of arsphenamine four days prior to death. No explanation was given for the fat emboli, but it is not at all probable that they were due to the toxic action of the drug.

From these cases it is obvious that intravascular fat has been demonstrated in deaths due to chemical poisons, but it is not as evident that the action of the chemical was the causative factor in the production of the embolism.

Natural Causes of Death.—Fat embolism has also been associated with many deaths from natural and nontraumatic causes. In the older literature, as cited by Scriba,[43] necrotic purulent foci and septic processes in general were supposed to produce severe grades of this condition. This was especially true when an osteomyelitis of the shaft of a long bone was the lesion in question, as it was usually accompanied by a rise of intra-osseous pressure which was supposed to force fat into the circulation. Others believed that the intravascular fat took its origin from fatty degeneration of thrombi or ulcerated areas on the vessel wall. At present, these theories are not taken seriously.

Jurgens [44] and Virchow,[25] considered that eclampsia caused fat embolism through multiple venous ruptures in the liver combined with fatty degeneration of the parenchyma cells which allowed liquid fat easily to enter the venous blood. Virchow, however, did not exclude injuries to the pelvic fat from childbirth as a cause of the emboli. It is possible that the fat emboli noted in connection with eclampsia may be due to some traumatic factor apart from the toxemia.

Diabetes mellitus, with lipemia, is supposed to produce intravascular fat similar to fat embolism, owing to the coalescence of the fine lipemic emulsion into larger droplets. Fischer,[45] Ebstein,[46] Saundby and Barling [47] described cases of this kind. Graham,[48] however, claimed

41. Winogradow, B.: Virchows Arch. f. path. Anat. **190**:92, 1907.
42. Burns, E. L., and Bromberg, L.: Am. J. Syph. **14**:43 (Jan.) 1930.
43. Scriba, J.: Deutsche Ztschr. f. Chir. **12**:118, 1880.
44. Jurgens: Berl. klin. Wchnschr. **23**:519 (Aug. 2) 1886.
45. Fischer, Bernhard: München. med. Wchnschr. **69**:814 (June 2) 1922.
46. Ebstein, W.: Virchows Arch. f. path. Anat. **155**:571, 1899.
47. Saundby and Barling: Brit. M. J. **1**:781, 1882.
48. Graham, G. S.: J. M. Research **11**:459, 1907.

that there is no similarity between the microscopic picture of the intravascular fat in diabetic lipemia and true fat embolism. It is not at all evident that the fat droplets in cases of fat embolism are derived from a lipemic condition of the blood.

Several investigators, including Katasa,[49] Olbrycht,[33] Weingarten,[30] Lehman and McNattin,[50] examined the lungs for fat embolism during a large number of routine necropsies in cases not associated with severe trauma. A definite proportion of positive observations were recorded, the highest of which was 50 per cent (Lehman and McNattin) and the lowest 7 per cent (Katasa).

Many of Katasa's series showed definite disease of the kidneys, and he was inclined to see a connection between the renal lesion and fat embolism. As Weingarten noted, however, care was not taken to exclude definitely slight traumas of different sorts, hypodermic injections of therapeutic oils and the like, which would be sufficient to account for the slight degree of fat embolism that was found.

Freak cases, interesting pathologically but of slight clinical importance, have been reported. Heitzmann [51] mentioned the instance of a man who died of gangrene of the lung following pneumonia; at necropsy fat emboli were found in the capillaries and the arterioles of the spleen and kidney, but not in the lung. This was explained by the fact that fatty débris had been aspirated from the gangrenous area through the pulmonary vein and transported to the left side of the heart and the arterial system. Groendahl [34] described fat emboli confined to the radicles of the portal vein in the liver, which he believed originated in one instance from a fat necrosis of the pancreas, and in another from trauma to the mesenteric fat involved in intussusception of the intestines.

A perusal of the literature suggests that while fat embolism is most often the result of injury to adipose tissue, examples of this condition have been recorded in which the history of trauma was not clear. The question then arises concerning the origin of the intravascular fatty globules; are they or are they not always the result of trauma?

An attempt was made to answer this question by studying a series of 246 necropsies, which occurred among the routine examinations of the Office of the Chief Medical Examiner of New York City. Sections of the lungs and kidneys from each necropsy were preserved in a solution of formaldehyde, sectioned on the freezing microtome and stained with sudan III. The sections were examined under the microscope for

49. Katasa, A.: Cor.-Bl. f. schweiz. Aerzte **47**:545 (May 5) 1917.

50. Lehman, E. P., and McNattin, R. F.: Fat Embolism, Arch. Surg. **17**:179 (Aug.) 1928.

51. Heitzmann: Centralbl. f. allg. Path. u. path. Anat. **28**:405 (Aug. 31) 1917.

fat emboli, and the diagnosis was made only when it could be definitely determined that the globule of intravascular fat was blocking the lumen of the arteriole or capillary.

The lungs and kidneys were chosen for this purpose because the presence of emboli in the lungs showed definitely that the liquid fat had entered the pulmonary circulation, while their presence in the kidney served as a convenient indication that the systemic circulation had been invaded.

The interpretation of results was necessarily qualitative. In the sections from the lung five degrees of fat embolism were recorded: (1) very slight, (2) slight, (3) moderate, (4) severe and (5) fatal. The degree was designated as very slight and slight when fat emboli

TABLE 1.—*Degree of Pulmonary Fat Embolism in Various Types of Injury*

Injuries	Negative Results	Very Slight	Slight	Moderate	Severe	Fatal	Total
Fractures of skull	8	5	8	3	0	0	24
Fractures of skull and ribs	2	3	1	0	0	0	6
Fractures of skull, ribs and clavicle	0	0	5	0	0	0	5
Fractures of skull and lower extremity	1	1	4	0	0	1	7
Fractures of femur	5	0	1	2	1	1	10
Fractures of pelvis	3	2	1	10	3	0	19
Fractures of tibia and fibula	5	2	2	0	2	1	12
Multiple fractures of lower extremity	1	0	0	3	1	0	5
Fractures of ribs and lower extremity	0	1	0	3	2	0	6
Fractures of ribs	0	0	4	2	0	0	6
Fractures of upper extremity	0	1	3	2	1	0	7
Injuries to soft parts of leg	2	1	0	1	0	0	4
Fractures of spine	1	0	2	4	0	0	7
Fractures of lower jaw	1	0	0	0	0	0	1
Bullet wounds	6	2	0	1	0	0	9
Stab wounds	6	0	0	0	0	0	6
Internal injuries	2	2	3	1	0	0	8
Scalp laceration	1	0	0	0	0	0	1
General lacerations	2	0	0	0	0	0	2
Manual strangulation	3	0	0	0	0	0	3
Head injury with subdural hemorrhage	3	0	0	0	0	0	3
Contusion of anterior abdominal wall	0	0	0	1	0	0	1
Operations	10	0	0	0	0	0	10
Orthopedic operations	0	0	0	1	1	0	2
Total	62	20	34	34	11	3	164

were found only occasionally in the section; as moderate when the emboli were numerous but did not occur in alarming numbers, and as severe and fatal when the embolism was excessive and dangerous to life.

Fat emboli were found in the kidneys only in a few cases of the severe and fatal types. They were never present when the lungs showed only a mild grade of embolism. They are not listed in the tabulations.

No attempt was made to demonstrate fat in the blood of the pulmonary artery macroscopically by the method described by Bacon and LeCount.[52] The conditions under which the necropsies were performed rendered the production of artefacts only too likely and would have given too many erroneous results.

52. Bacon, L. H., and LeCount, E. R.: Automobile Injuries, Arch. Surg. **18:** 769 (March) 1929.

The 246 necropsies are separated into those associated with physical trauma, which numbered 164 cases, and those not associated with physical trauma, which numbered 82 cases. The first category is represented in table 1. The age and sex are not shown on the chart as the figures had little bearing on the results, and it is sufficient to mention that the male sex predominated and that the age at which the injuries were most prevalent was from 20 to 60 years.

According to table 1, the type of injury had a great deal of influence on the production of the emboli. Fractures of the skeleton, especially of the bones of the lower extremity, were marked by a greater incidence and a more severe grade of fat embolism than were other forms of trauma. As a general rule, the more severe the violence that produced the fracture the more consistent was the appearance of the emboli in the lungs.

TABLE 2.—*Degree of Fat Embolism in Fractures of the Lower Extremity*

	Negative	Very Slight	Slight	Moderate	Severe	Fatal	Total
Patients dying at scene of accident	1	2	0	3	0	0	6
Patients dying in 1 to 24 hours	1	2	4	11	5	0	23
Patients dying in 1 to 7 days	3	1	4	4	4	3	19
Patients dying in 7 to 14 days	3	0	0	0	0	0	3
Patients dying in 14 to 21 days	1	1	0	0	0	0	2
Patients dying after 21 days	6	0	0	0	0	0	6
	15	6	8	18	9	3	59

In the cases of fracture of the lower extremity, there were indications that most of the fat embolism was caused by aspiration of liquid fat into the circulation at the site of injury through the torn ends of the small veins. Investigation of the region of the fracture, especially in persons who had survived the violence only a few minutes, disclosed from 40 to 60 cc. of liquid fat mixed with blood around the ends of the broken bones. When the patient had lived longer the quantity of the extravasation was sometimes the same, but was usually much less. Apparently the amount taken into the circulation varied with the individual case, because fractures similar in other respects showed widely different degrees of fat embolism. The protective mechanisms of the organism against the aspiration of fat into the circulation, such as collapse of the veins or closure of the veins by the processes of repair, were more efficient in some instances than in others.

A measure of the efficiency of these mechanisms can be noted in table 2, in which fifty-nine cases of fracture of the lower extremity are listed. About 80 per cent of these were negative for fat emboli, or showed only a moderate number, while only 20 per cent displayed a serious degree of embolism.

The relationship between the degree of fat embolism and the length of time the patient lived after the injury is shown in table 2. Of forty-eight patients who died during the first week after the trauma occurred, forty-three had fat emboli and five did not. The more severe grades of the condition were found in those who lived from one to seven days. After the first week only one case of slight degree was noted. These facts suggest that the greatest amount of fat enters the circulation in the first seven days after the fracture, but that after this interval it is removed from the vessels in some manner.

In injury other than fracture, only six cases showed fat embolism of moderate grade or over. Of these one was the result of an injury to the soft parts of the leg, one was due to a ruptured liver, two were the result of orthopedic manipulations, and one was associated with a contusion of the anterior abdominal wall followed by a laparatomy. In

TABLE 3.—*Results of Examination for Fat Emboli in Absence of Physical Trauma*

	Negative	Positive	Total
Electrocution	1	0	1
Burns	3	0	3
Chemical poisons	16	1	17
Cases showing gas decomposition	2	0	2
Natural causes of death	53	6	59
			82

the sixth case a bullet wound of the retroperitoneal tissues and the inferior vena cava macerated the fat cells and allowed the liquid fat to gain entrance to the circulation through the hole in the vein. In spite of the fact that the patient died in a few minutes from hemorrhage, a moderate grade of pulmonary fat embolism was found.

In this series there was no instance of fat embolism that could be attributed to jarring of the skeleton. There was one case, however, in which lesions similar to those described by Frauendorfer [11] were noted in the bone marrow. A man, aged 45, fell from a height, fractured his left thigh bone and died in a few minutes of shock. The right femur was not broken, but section through the shaft disclosed hemorrhagic areas, from 1 to 2 mm. in size, distributed through the fatty marrow. On microscopic examination, the fatty tissue was found to be torn from the bony trabeculae in these areas, with consequent extravasation of red blood cells.

The eighty-two cases that were not associated with physical trauma are listed in table 3.

The seven positive results were examples of a very slight fat embolism in the lungs. The kidneys were normal in every case.

The large number of negative results coupled with the few positive observations suggests that when death is not connected with physical trauma a fat embolism of a serious grade is not likely to develop.

The cases of burns were caused by flame in two instances and were of the third degree. The other burn was due to scalding water.

The cases of poisoning included eight of acute alcoholism, three of chronic alcoholism, one of alkaline corrosion of the stomach, one of arsphenamine poisoning, and one of illuminating gas poisoning, all of which were negative for fat emboli. The only positive result consisted of a very slight degree of fat embolism in a case of methyl alcohol poisoning, and the connection between the two conditions was dubious.

Of the fifty-nine cases in which death was due to natural causes, fifty-three were negative, and six positive, for fat emboli.

The cases giving negative results included ten of heart disease, four of chronic nephritis, three of advanced liver disease, twelve of pulmonary disease, six of cerebral conditions, six of sepsis following abortion, one of eclampsia, one of diabetes mellitus, two of pernicious anemia, one of pyelonephritis, one of mesenteric thrombosis, three of general carcinomatosis, one of intestinal obstruction and one case each of malnutrition and encephalitis, respectively, in children.

The cases giving positive results comprised two of chronic nephritis, one of pachymeningitis interna hemorrhagica, one of abscess of the brain, one of chronic duodenal ulcer and one of sepsis due to abortion.

The reason for the pulmonary fat emboli in these cases must be a matter of speculation, as a complete history could not be obtained. It is conceivable, however, that a slight injury of adipose tissue somewhere in the body during convulsions or therapeutic injections of oily liquids into a small vein by accident can produce this condition on occasion. In any event, the degree of the embolism in these cases was so slight as to be of little clinical importance.

The only conclusions to draw from these facts are that from 12 to 14 per cent of cases of nontraumatic death may show a slight grade of fat embolism. As a result, a slight grade of fat embolism cannot be considered a reliable indication of trauma. On the other hand, a severe or moderate grade of fat embolism is the result of an intravital injury and when demonstrated post mortem is sufficient proof that the trauma occurred prior to death.

FAT EMBOLISM IN HUMAN PATHOLOGY: CLINICAL SIGNS AND PATHOLOGIC LESIONS

After an injury when fat is absorbed into the blood the first stopping place is the lungs. These organs, as Fischer [53] pointed out, are capable of accommodating large numbers of fat emboli. Their reserve capacity is so great that it is only in severe cases that the embolism obstructs the pulmonary circulation. When this occurs, two eventualities present

53. Fischer, Bernhard: Verhandl. d. deutsch. path. Gesellsch. **17**:279, 1914.

themselves, as Payr [54] first noted: 1. The patient will die as the result of asphyxia from the emboli in the lungs. 2. The emboli will be driven through the pulmonary vessels into the arterial side of the circulation where they will cause death by involving such important organs as the brain, heart and kidneys. Payr [54] termed the first outcome pulmonary fat embolism and the second, cerebral fat embolism.

PULMONARY FAT EMBOLISM

The symptoms of pulmonary fat embolism are referable to the obstruction in the pulmonary circulation which causes a marked decrease in the respiratory interchange in the alveoli. As a result the oxyhemoglobin content of the red blood cells is lessened and the carbon dioxide content of the plasma is increased. At the same time, the right side of the heart becomes engorged and is unable to force the blood onward. The supply of blood to the left side of the heart is curtailed, and the arterial blood pressure falls. The whole organism tends to suffer from the deficient oxygenation of the red blood cells and the disability of the circulation. In the end the interchange of oxygen in the tissues is damaged.

Groendahl [34] recognized two clinical varieties of pulmonary fat embolism: 1. The first type is marked by a violent onset of dyspnea attended by marked cyanosis and edema of the lungs which comes on suddenly a few hours after the injury. Death in these cases is rapid and is attributed to the fact that after the trauma large amounts of fat are absorbed rapidly. 2. The second type is slower in its development. An appreciable interval of from several hours to several days intervenes between the injury and the onset of the symptoms. After the trauma the patient may be quiescent or at the most show a few signs of restlessness and anxiety. A persistent cough then appears, accompanied by blood-tinged sputum, dyspnea, cyanosis and signs of edema. Toward the end the respiration becomes stertorous and passes gradually into the Cheyne-Stokes type. In this final stage coma develops which is referable in part to the asphyxia and in part to a disturbance of the cerebral circulation.

According to Groendahl,[34] the pulmonary type of fat embolism is likely to develop in patients whose myocardium is weak, especially on the right side of the heart. Many of these cases are found in elderly persons possessing, in addition to the cardiac disability, emphysematous lungs the capillaries of which are smaller than normal and so are more easily blockaded by the embolic fat. Groendahl claimed that dilatation of the right ventricle is found at necropsy in such cases. He contended that younger and stronger persons with an efficient heart muscle are

54. Payr, E.: Ztschr. f. orthop. Chir. **7**:338, 1900.

more apt to force the fat onward into the general circulation, and are less likely to succumb to asphyxia.

The principal lesions in pulmonary fat embolism are in the lungs. On macroscopic examination these organs appear voluminous and cyanotic and show areas of aeration mingled with darker areas of congestion and edema, which are characteristic of asphyxial conditions in general. Small hemorrhages may occur in the pleura or in the septums of the lung; groups of alveoli may be filled with blood and appear under the pleura as small hemorrhagic foci. These lesions are supposed to be caused by the back pressure in the pulmonary circulation which ruptures small pulmonary vessels.

On microscopic examination fat emboli can be demonstrated in the arterioles and capillaries of the lungs in large numbers. In the arterioles they appear as spherical or ovoid globules blocking the lumen. If the vessel branches at this point, the emboli may be forced into a dendritic or stellate form. In the capillaries the fat is seen in the form of small ovoid or spherical emboli which may be so numerous that the alveolar walls are outlined as if by strings of beads. As noted by Wegelin,[55] all parts of the lung are about equally involved.

As a rule, the capillaries contain a large number of fat emboli only in persons who have had severe asphyxial symptoms during life. After an injury the fat first lodges in the arterioles, where it stays unless the pulmonary circulation is impeded by the embolism. When this occurs, the fat globules in the arterioles are forced into the capillary network and are broken up into smaller globules in the process. Not infrequently a small amount of the fat is forced further on into the systemic circulation, so that in cases of severe pulmonary involvement isolated emboli can be found in the finer vessels of the kidney, myocardium and cerebral cortex.

Aside from the embolism in the vessels the lungs show fluid in the alveoli, in which are red blood cells, leukocytes, large spherical cells and the like. In some instances the exudate may become frankly that of a bronchopneumonia. In rare instances fibrinous thrombi may form ante mortem in some of the smaller arteries as a result of the stasis in the pulmonary circulation.

The presence in the alveoli of large spherical cells containing fat granules is noted often and similar cells are found in the sputum during life. Elting and Martin [56] regarded this as an important diagnostic sign. In the absence of fat embolism, however, similar cells have been found in the lungs in various toxic conditions. For this reason, their presence cannot be considered pathognomonic.

55. Wegelin, C.: Schweiz. med. Wchnschr. **4**:133 (Feb. 8) 1923.
56. Elting, A. W., and Martin, C. E.: Ann. Surg. **82**:336 (Sept.) 1925.

Several examples of pulmonary fat embolism, of severe enough grade to be clinically important, were found in the necropsy material. They could be divided arbitrarily into two categories: (1) cases in which the fat embolism in the lungs was severe enough to contribute to the death of the patient, if associated with some other morbid condition, and (2) cases in which the grade of fat embolism was so marked that it caused death by itself.

Unfortunately, in all instances an adequate clinical history was not obtainable, but the postmortem observations indicated the true condition sufficiently well. Category 1 was represented by three cases.

CASE 1.—A white woman, aged 70, sustained a compound fracture of the left tibia and fibula in an automobile accident. She survived the injury four days. At necropsy, an infected compound fracture of the left leg was found, and a few of the ribs were fractured. Signs indicated that the chief cause of death was septic poisoning. However, there were numerous fat emboli in the arterioles and capillaries of the lungs and a few in the cerebral cortex and glomeruli of the kidneys. The fat embolism in all probability contributed to the fatal result through its effect on the pulmonary circulation.

CASE 2.—A white man, aged 75, was struck by an automobile and suffered a fracture of the left tibia and fibula, the left clavicle and eight ribs on the left side. He died about twenty-four hours after the injury. A clinical history of his symptoms was not obtainable. Necropsy revealed all the signs of a marked general arteriosclerosis and, in particular, a marked fibrosis of the left ventricle. The lungs were congested and edematous. Microscopic examination showed numerous fat emboli in the arterioles and capillaries of the lung, and a few in the cerebral cortex and the glomeruli of the kidneys. It was obvious that the embolism was severe enough to embarrass the circulation already damaged by arteriosclerotic processes.

CASE 3.—A man, aged 39, was struck in the abdomen by an automobile. He entered the hospital complaining of rigidity and tenderness in the upper left quadrant. The symptoms strongly suggested an internal abdominal injury, so a laparotomy was performed under ether anesthesia about two hours after admission. A contusion of the left rectus abdominalis was noted, but the internal organs were intact and the peritoneal cavity was normal. After the operation, a hypostatic pneumonia developed and the patient died of this complication two and a half days after he sustained the trauma.

Necropsy disclosed the contusion of the abdominal wall, the laparotomy wound and a severe hypostatic pneumonia of both lungs. The skin and tissues were slightly icteric and more or less dehydrated. It was evident that the patient was suffering from considerable toxemia. Microscopic examination revealed numerous fat emboli in the arterioles and capillaries of the lung, but there were none present in the brain, heart or kidneys. There were indications, however, that the right side of the heart had been somewhat embarrassed by the embolism in the lungs, for in places the white matter of the cerebral cortex showed red dots, the size of a pinhead and circular in outline, which on section were found to be engorged veins. They were produced by back pressure in the venous system, combined with the toxemia from the pneumonia, which had the effect of causing a marked distention of the vessels.

In all these cases the degree of fat embolism was about the same. Most of the arterioles were filled with fat globules, and here and there the walls of from two to four adjacent alveoli showed distinct rows of fat globules in the capillaries. It is possible that in itself the process might not have resulted fatally, but in combination with other pathologic conditions the embolism caused enough embarrassment of the pulmonary circulation to hasten the death of the patient.

Many investigators consider that fat embolism not infrequently complicates other conditions to produce death; in general, this is the view expressed by Payr,[54] Groendahl [34] and Frauendorfer.[11] Payr,[19] who investigated fat embolism after orthopedic manipulations, was of the opinion that the fatal result was attributable to the fat emboli acting in conjunction with status lymphaticus. Similarly, in the study of traumatic shock, Gold and Loeffler [57] reached the conclusion that the chief rôle of fat embolism was to increase the deleterious effects primarily attributable to the shock.

The second type of pulmonary fat embolism comprised those cases in which the process was so marked that it was capable of causing death.

CASE 4.—This case was described previously.[58] A man, aged 62, was struck by an automobile and sustained fractures of the right femur, right tibia and right fibula. He died thirty-six hours later in an asthmatic attack.

At necropsy, there was a moderate degree of coronary arteriosclerosis, chronic nephritis, senile atrophy of the brain and hypertrophy of the prostate. The lungs were large and edematous. Microscopic examination disclosed a marked capillary fat embolism of the alveolar walls, to such a degree that the alveoli in places were practically outlined by fat droplets. A few fat emboli were found in the brain, kidneys and heart muscle, but not in sufficient number to produce a lesion.

CASE 5.—A white man, aged 45, was found in a hallway at the foot of the stairs. There was no history of a definite trauma, but on admission to the hospital the patient was in coma, was deeply alcoholic and showed lacerations of the scalp, a fracture of the left fibula and a luxation of the inner end of the left clavicle. For the first ten hours after admission he was irrational but recovered consciousness sufficiently to tell his name and address. At this time it was noted that his respirations became more difficult and rapid, and his pulse rate increased steadily up to the time of his death, thirty-one hours after admission.

Necropsy disclosed a well developed adult male with a number of injuries. The left fibula was broken in two places, and the internal malleolus of the left tibia was broken across. There was a fracture of the sternum and of ribs 2, 3, 4, 5 and 6 on the left side anteriorly. These fractures were simple. There was a luxation of the inner end of the left clavicle. In addition there was a subcutaneous separation of the skin in the right popliteal space from the muscles through the fatty layer over an area 3 by 4 inches (7.6 by 10.1 cm.). The skull showed a small linear fracture posteriorly, but the brain was not lacerated.

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57. Gold, E., and Loeffler, E.: Ztschr. f. d. ges. exper. Med. **38**:155, 1923.

58. Vance, B. M.: Fatal Fat Embolism, Arch. Path. **7**:554 (March) 1929; Proc. New York Path. Soc., Dec. 15, 1928.

The internal organs showed the lungs to be heavy and edematous, with areas of atelectasis posteriorly, and a small patch of pneumonia in the anterior part of the left upper lobe, about 1 inch (2.5 cm.) in diameter. The heart was large but normal. The foramen ovale was not patent. The stomach was distended with a large quantity of foul-smelling fluid, but the rest of the gastro-intestinal tract was normal. The other internal organs were practically normal.

On microscopic examination the lungs were filled with a large number of fat emboli which crowded the capillaries and arterioles to such an extent that numerous alveoli were outlined by the lines of globular emboli (fig. 1). Considerable

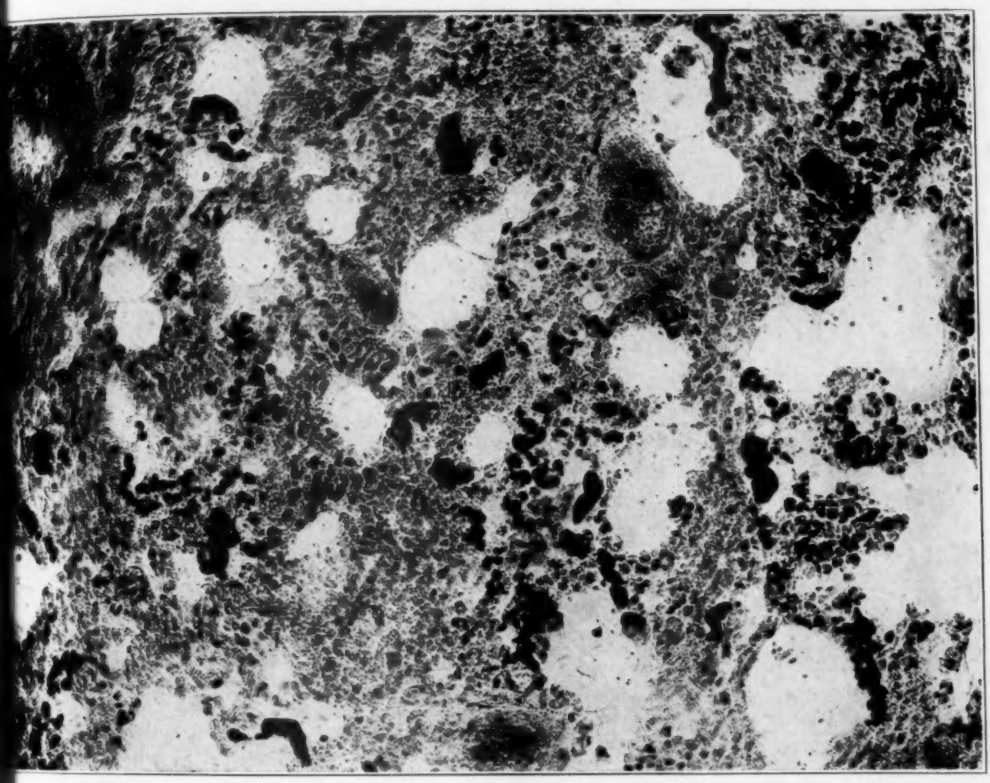

Fig. 1 (case 5).—Section of the lung in pulmonary fat embolism. Osmic acid stain.

edematous fluid was present in the alveolar lumen. A moderate number of emboli were found in the cerebral cortex, the myocardium and the glomeruli of the kidney.

In this case it is obvious that the embolism was the cause of death and that the pneumonia was so slight that it was merely a complicating and terminal factor.

SYSTEMIC OR CEREBRAL FAT EMBOLISM

In a few patients fat emboli may pass in large numbers from the pulmonary circulation into the arterial circulation, and hence be dis-

tributed to all the organs of the body, especially the brain, heart and kidneys. The most prominent symptoms are caused by the action of this process on the brain, and so the term cerebral fat embolism has been applied to the condition by Payr,[54] Groendahl [34] and others.

The fat is supposed to be transferred from the venous circulation to the arterial vessels in two ways:

1. It is transferred through some opening which enables the right side of the heart to communicate with the left side, which in most instances is the foramen ovale. According to Kaufmann,[59] the foramen is present in 33.33 per cent of all cases that come to necropsy, and is located in the interauricular septum. It can generally be demonstrated as a narrow slit, penetrating the septal wall obliquely, so that under normal conditions it is doubtful if blood ever passes through it from one circulation to the other. Certain investigators, including Naville and Fromberg [60] and Frauendorfer,[11] however, have expressed belief that in cases of fat embolism liquid fat may be forced from the right auricle through the foramen ovale into the left auricle. As Frauendorfer explained it, the blocking of the pulmonary vessels by the embolism raises the pressure in the pulmonary artery and the right side of the heart, and the foramen ovale is opened so that blood and oil pass into the left side of the heart. It cannot be proved, of course, that this method of transfer is impossible, but it has been shown that a cerebral fat embolism of a severe grade can occur in the absence of a patent foramen ovale or any other similar channel.

2. It is probable that the most important, if not the only, method of transference of the oil from the venous side to the arterial side is through the pulmonary capillaries into the pulmonary veins. As Groendahl [34] pointed out, the typical examples of this process are to be found in sthenic persons, whose right ventricle is strong enough to force the obstructing fat globules through the capillaries of the lung, which are relatively large and easily distensible. The process is greatly enhanced, according to Siegmund,[5] by any subsequent trauma which may befall the patient. In his series of cases of fracture among the wounded in the battle field, the jarring inflicted on the patients in transporting them from one place to another undoubtedly forced the fat from the pulmonary capillaries into the arterial blood and caused systemic fat embolism.

After the fat has reached the left side of the heart, it is distributed immediately to the different parts of the body, blocks the arterioles and

59. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, G. Reimer, 1911.

60. Naville, F., and Fromberg, C.: Arch. de méd. expér. et d'anat. path. **25**: 405 (July) 1913. Fromberg, C.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:23, 1913.

capillaries, and causes definite pathologic changes in the various organs. Because its arterial blood supply is extensive, the brain receives a large proportion of the fat emboli. These cause changes in the brain substance and evoke the clinical picture that Groendahl [34] and others have described under the name of cerebral fat embolism.

The symptoms of this complication can be divided into three stages which at times can be differentiated sharply but in other instances shade imperceptibly into one another:

(*a*) There is first the period between the trauma and the first appearance of symptoms, which averages from forty-eight to sixty hours in length, but which may vary from four hours to nine days. In this stage the patient is free from disturbing complications and is relatively comfortable.

(*b*) The soporific stage occurs next and is usually ushered in by premonitory signs, such as dyspnea, restlessness, precordial pains and increased pulse rate. Groendahl [34] suggested that this is the stage when the fat is passing through the pulmonary capillaries into the arterial blood and that it is probably referable to the difficulties experienced by the right side of the heart during this process. Shortly after, symptoms of cerebral origin occur, such as insomnia, loss of memory, disorientation and a slight delirium, which in alcoholic patients may become true delirium tremens. After a variable interval, the patient sinks into a stuporous condition and passes gradually into the last stage, that of coma.

(*c*) The coma becomes deeper and deeper, and is attended by various neurologic signs in many instances. The papillary and corneal reflexes gradually disappear. Signs of cortical irritation, such as muscular rigidity, clonic convulsions, tonic contractures and trismus, may present themselves. Paralytic involvement of muscular groups, especially around the arms and shoulders, occasionally occurs. As the coma grows deeper, there may be a general flaccidity of all muscles, followed by paralysis of the sphincters. From 24 to 100 hours after the onset of the coma, death occurs in profound unconsciousness, heralded at first by small rapid respirations, which later change to the Cheyne-Stokes type. As a rule, signs of cerebral compression are absent from the clinical picture.

The onset of coma and the fatal result are referable directly to the fat emboli which literally pervade all parts of the central nervous system, especially the brain. The fat entering the cerebral vessels is broken up into small emboli and is lodged in the precapillary and capillary vessels of the cortex and white matter. It is not known whether the brain is involved by a single invasion of emboli or whether separate invasions occur from time to time. In either event the blocking

of the vessels by the globules causes distinct lesions of the brain substance, which are grossly and microscopically evident.

Macroscopic examination of the brain, as recorded by Groendahl,[34] Gauss,[1] Melchior,[61] Weimann [62] and others, discloses a varying grade of congestion of the brain substance, with numerous small petechial hemorrhages pervading the white matter of the brain and cord, especially the region of the centrum ovale in the vault of the cerebrum. The hemorrhages are the size of a pinhead, are usually grouped in colonies of from four to twelve and literally pepper the brain substance. Weimann [62] claimed that they may be so thick as to be almost confluent.

Under the microscope fat emboli can be demonstrated in arterioles and capillaries in all parts of the central nervous system including the cord, ganglions, membranes and choroid plexus. The most serious involvement takes place in the white and gray matter of the brain.

The gray matter is invaded the earliest and the most profusely by the emboli. Very few lesions can be demonstrated, however, as the capillary anastomoses are so extensive that the nutrition of the tissue is rarely impaired under normal conditions. The most that can be seen is the emboli filling the arterioles as sausage-shaped globules or as spherical bodies arranged in rows like beads. As Buerger [63] noted, it is only in brains already damaged by syphilis or by chronic alcoholism that definite lesions of the gray matter can be observed.

In the white matter the situation is different. The arterioles are end-vessels which branch in a dendritic fashion, and which communicate by scant capillary anastomoses. The embolus obstructing such a vessel effectively impairs the nutrition of the tissue that it supplies, and degenerative changes occur. Some of these changes result in petechial hemorrhages, and others appear as peculiar anemic areas of necrosis termed "rarefied areas."

The majority of investigators believe that the hemorrhages are minute infarcts caused by fat emboli in the cerebral arterioles, though there are differences of opinion concerning the exact method of production. Frauendorfer [11] attributed the hemorrhages to rhexis of the vessel wall by pressure from the embolus. Groendahl believed that the blood is extravasated from the capillaries in the healthy tissue surrounding the area of necrosis. Weimann [62] remarked, however, that it is not possible to tell just how much these various mechanisms may operate in every instance.

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61. Melchior: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **38**:178, 1924-1925.

62. Weimann, Waldemar: Deutsche Ztschr. f. d. ges. gerichtl. Med. **13**:95 (Feb.) 1929.

63. Buerger, L.: Med. Klin. **11**:996 (Sept. 5) 1915.

Toenniessen [64] was the only writer to offer another explanation for the production of the petechial hemorrhages. He said that they are not the result of emboli in the cerebral vessels, but are referable to a marked pulmonary fat embolism which causes back pressure in the superior vena cava and consequent rupture of the minute blood vessels in the brain. It is probable that a few hemorrhages may be produced in this fashion, but in most instances this mechanism is not important.

On microscopic examination a cross-section of the early stages of the petechial hemorrhages shows a fat embolus filling a small arteriole, while around the vessel is a circular zone of necrotic brain tissue and around this a circular zone of extravasated red blood cells. From this appearance the name of ring hemorrhage has been applied to the lesion. Longitudinal sections of such a vessel show that the part of the arteriole that is distal to the embolus is capped by a conical covering of necrotic tissue surrounded, in turn, by the layer of red blood cells. The lesion is, in fact, a microscopic hemorrhagic infarct, and the extravasated blood is probably derived from the capillaries immediately surrounding the necrotic area, as Groendahl [34] has already mentioned.

Later the processes of inflammation and repair occur. Inflammatory cells like leukocytes and lymphocytes invade the necrotic tissue; the ganglion cells and axis cylinders disintegrate; hyaline bodies, amyloid bodies and hemosiderin granules make their appearance. Finally large cells of glial origin appear. The end-result of the process is the removal of the embolus and the formation of a scar. This was observed in experimental animals by Paul and Windholz [65] but it has not been fully described in human tissues.

In some instances the fat emboli in arterioles supplying a portion of the brain substance cause areas of necrosis without hemorrhage, which have been termed "rarefied areas." As a rule, they are minute, irregularly ovoid and, in the early stages, translucent and meshlike. The blood vessels in the immediate surroundings are filled with fat emboli. Apparently the process is a sudden and intense destruction of the medullary sheaths due to anemic necrosis, with preservation of the axis cylinders, while at the same time lymphatic fluid pours in from the surrounding tissues and widens the meshes. Later the process of repair sets in and glial cells tend to fill in the spaces. The absence of a hemorrhagic zone around this lesion is probably due to the fact that the capillaries in the surrounding healthy tissue are blocked off from the necrotic zone by the embolism and so blood is not extravasated. The lesion is in reality a minute anemic infarct of the brain.

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64. Toenniessen, Otto: München. med. Wchnschr. **68**:1280 (Oct. 7) 1921.

65. Paul, Fritz; and Windholz, Franz: Mitt. a. d. Grenzgeb. d. Med. u. Chir **38**:614, 1924-1925.

Kidney.—The kidneys are involved almost invariably in cases of systemic fat embolism though they fail to show characteristic changes on microscopic examination. The principal lesion consists of large snakelike or pretzel-like emboli filling the capillary coils of the glomeruli. They occur less often in the vasa afferentia.

Other changes occur less consistently, and there is considerable doubt whether they are due to the emboli or to other processes. Occasionally fine fatty granules fill the cytoplasm of the epithelial cells of the convoluted tubules; these were attributed by Groendahl [34] to the curtailment of the blood supply by the fat plug in the glomeruli, and by Scriba [43] and Buerger [63] to toxic action initiated by the embolism. Buerger described small hemorrhages in the kidney substance and thrombus formation and necrosis around the embolus which he also attributed to the action of toxic products set free by saponification of the embolus.

Several investigators have expressed the belief that the presence of fat emboli in the kidney will cause uremic symptoms and anuria. Busse [9] described a case of anuria that was complete for about forty-eight hours prior to death. Paul and Windholz [65] claimed that in their case uremia, albuminuria, urinary casts and a gangrenous enteritis of uremic origin developed. Others, including Groendahl,[34] doubted that fat embolism can produce such extreme manifestations because the emboli do not involve all the glomeruli. The experiments of Paul and Windholz and of Flick and Traum [66] indicated, however, that a certain degree of interference with the excretory function of the kidneys can be caused by the glomerular lesions. It is probable that in a patient whose kidneys are already diseased, the embolic process may cause uremia or anuria to develop, though it might not have a like effect on comparatively normal organs.

Lipuria, or fat in the urine, has been described in many cases by Scriba [43] and others. There is considerable divergence of opinion concerning the way in which the fat is excreted. Scriba regarded it as a filtration into Bowman's capsule through the intact vessel wall. Ribbert [67] said that the fat ruptures the glomeruli and thus gains access to the tubules, or it appears as the result of secondary degeneration and destruction of the tubular epithelium. Some observers, including Scriba,[43] consider the excretion through the kidneys one of the most important ways of getting rid of the intravascular fat; others, including Groendahl,[34] regard it as a process of minor importance and claim that fat cannot be demonstrated in the lumen of the tubules in cases of fat embolism. At the present time, however, lipuria is held by some to be a certain diagnostic sign of fat embolism, even though

66. Flick, K., and Traum, E.: Deutsche Ztschr. f. Chir. **222**:274, 1930.
67. Ribbert (footnote 10, first reference).

the details of the process are still a trifle obscure. Its true significance can be determined only by future investigations.

Heart.—In systemic fat embolism the heart is invaded rather frequently and on macroscopic examination shows numerous streaky hemorrhages, from 1 to 3 mm. in diameter, in the ventricular muscle. At times the larger hemorrhages contain a yellowish-white centrum in the midst of the dark red streak. Under the microscope the arterioles and capillaries are seen to be filled with sausage-shaped emboli, and on occasion the peculiar ladder-like anastomoses of the myocardial capillaries can be demonstrated.

The adjacent muscle fibers are peppered with minute fat granules and are smaller than the normal fibers. Numerous red blood cells surround the emboli and infiltrate between the fibers. The lesion is a true hemorrhagic infarct of minute size. Permanent scars due to this process have not been described, however.

When the emboli appear in large numbers the cardiac muscle is probably weakened, as Colley [16] suggested, but it is difficult to estimate their influence on the clinical symptomatology. Similar lesions in the skeletal muscles have been described by Warthin.[24]

Skin and Mucous Membranes.—The skin of the upper part of the chest, the shoulders and the anterior part of the neck are frequently peppered with small dark red petechial hemorrhages, the size of a pin head, and usually gathered in groups of from four to twelve, which make their appearance about the time the patient lapses into stupor. These changes are referable to a fat embolism of the arterioles of the dermis, which in some way causes an extravasation of red blood cells around the affected vessel. The process is comparable to similar lesions in the heart and brain. When the hemorrhages are discovered during life they are an excellent aid in diagnosis, as in the cases described by Groendahl [34] and others. After a lapse of several days they tend to disappear. Similar petechial hemorrhages have been noted on the conjunctivae by Busch [3] and Frauendorfer,[11] on the soft palate by Wilke [68] and in the gastro-intestinal tract and bladder by Naville and Fromberg.[69] As a rule, these petechiae do not produce permanent lesions. Schridde [70] described multiple small erosions of the mucous membrane of the stomach, which he attributed to fat emboli.

Liver.—On macroscopic examination the liver does not show any noteworthy changes. Microscopic examination discloses fat emboli in the capillaries and occasionally fatty granules in adjacent parenchyma cells and Kupffer's star-shaped cells. Clinically there are no symptoms

68. Wilke: München. med. Wchnschr. **60**:1970 (Sept. 2) 1913.
69. Naville and Fromberg (footnote 60, first reference).
70. Schridde: Verhandl. d. deutsch. path. Gesellsch. **11**:234, 1907.

that can be referred to this embolism of the liver, though the experimental work of Paul and Windholz [65] indicated that the glycogen metabolism shows some disturbance.

The spleen shows fat emboli in the outer rim of the splenic follicle, but the parenchyma of the organ is not damaged, as a rule.

The suprarenals, pancreas and thyroid contain fat emboli, but aside from the presence of fat granules in the adjacent parenchyma cells and occasional extravasations of red blood cells, few other changes have been described.

In systemic fat embolism the lungs show the lesions that have already been described under pulmonary fat embolism.

Two examples of systemic fat embolism were encountered among the routine necropsies.

Case 6.—A white woman, aged 65, was struck by an automobile; the shafts of the right femur, right radius and right ulna were fractured. She was admitted to a hospital in coma, and remained so until her death two days later. A more detailed history of her clinical course could not be obtained.

Necropsy disclosed the fractures of the extremities already mentioned, and in addition, lacerations of the left side of the forehead. There was also a short fracture of the left anterior fossa of the skull. The brain was not lacerated, but showed numerous petechial hemorrhages grouped in colonies of from four to ten, scattered throughout the white but not the gray matter.

The myocardium showed a moderate grade of brown atrophy and was permeated by numerous streaky hemorrhages, from 2 to 4 mm. in diameter. There was a small circular opening, 3 mm. in diameter, in the fossa ovalis allowing free communication between the right and left auricles.

The lungs were congested, well aerated and normal aside from a small amount of atelectasis posteriorly. The other organs were normal. Petechial hemorrhages could not be found on the skin.

Microscopic examination disclosed a widespread systemic fat embolism. As the histologic features were similar to those in case 7, the description will be given later.

Case 7.—A strongly built white man, aged 65, was struck by an automobile and admitted to the hospital in coma. A severe contusion of the right eyelids, a Pott's fracture of the right fibula and compound comminuted fractures of the lower end of the left tibia and fibula were found. Blood was noted issuing from the nose and the left ear canal. A lumbar puncture revealed blood in the spinal fluid. A tentative diagnosis of fracture of the skull was made from these observations.

On admission to the hospital the blood pressure was 154 systolic and 88 diastolic. Six hours later it dropped to 94 systolic and 65 diastolic. An injury of the brain was suspected, but a satisfactory neurologic examination could not be made because of the condition of the patient. He remained in coma while in the hospital and died two days and eight hours after admission.

Necropsy disclosed a strongly built man, aged 65, who showed the external injuries already described. In addition there were numerous petechial hemorrhages of the front part of the chest, neck and shoulders; these occurred in groups of from four to twelve. Similar hemorrhages were noted in the conjunctivae.

The skull showed a linear fracture in the left middle fossa which, however, was not attended by a laceration of the brain or any other intracranial injury. There were numerous petechial hemorrhages, the size of a pinhead, scattered in groups through the white matter of the brain, especially in the vertex of the cerebral hemisphere. There was none present in the gray matter. The cerebral arteries were slightly sclerotic.

The heart showed a slight hypertrophy and coronary arteriosclerosis. The myocardium was permeated by ovoid and flamelike hemorrhages, from 1 to 3 mm. in diameter. It is significant that a foramen ovale or other communication between the right and left sides of the heart was not present.

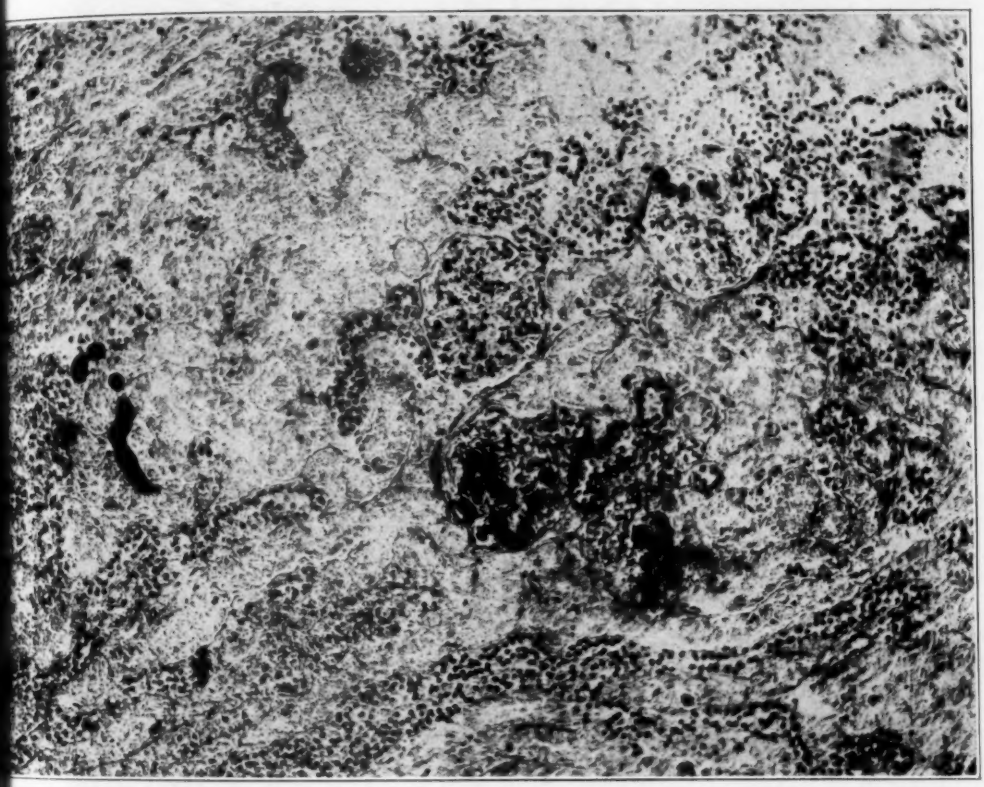

Fig. 2 (case 7).—Fat emboli in the glomeruli of the kidney. Osmic acid stain.

The lungs were heavy and voluminous but showed mainly congestion and edema.

The kidneys were normal, aside from a moderate grade of arteriosclerotic change.

On microscopic examination a widespread fat embolism of the lungs, brain and other organs was disclosed. The arterioles and capillaries of the lungs were filled with numerous fat plugs, which outlined the alveoli in many places.

The kidneys showed the characteristic snakelike and pretzel-like emboli in the glomerular coils, but no other noteworthy changes (fig. 2).

The myocardium disclosed numerous ovoid fat emboli in the arterioles and even in the capillaries, showing anastomoses in places. There was fatty degeneration and atrophy of the fibers immediately adjacent to the emboli and also hemorrhage between the muscle fibers. Some of these areas of embolism and degeneration were large.

The lesions in the brain were the most characteristic. Numerous ring hemorrhages and areas of rarefaction were found in the white matter adjacent to the fat emboli. In the gray matter numerous emboli were present in the arterioles, but lesions of the brain tissue were noted only occasionally (figs. 3 and 4).

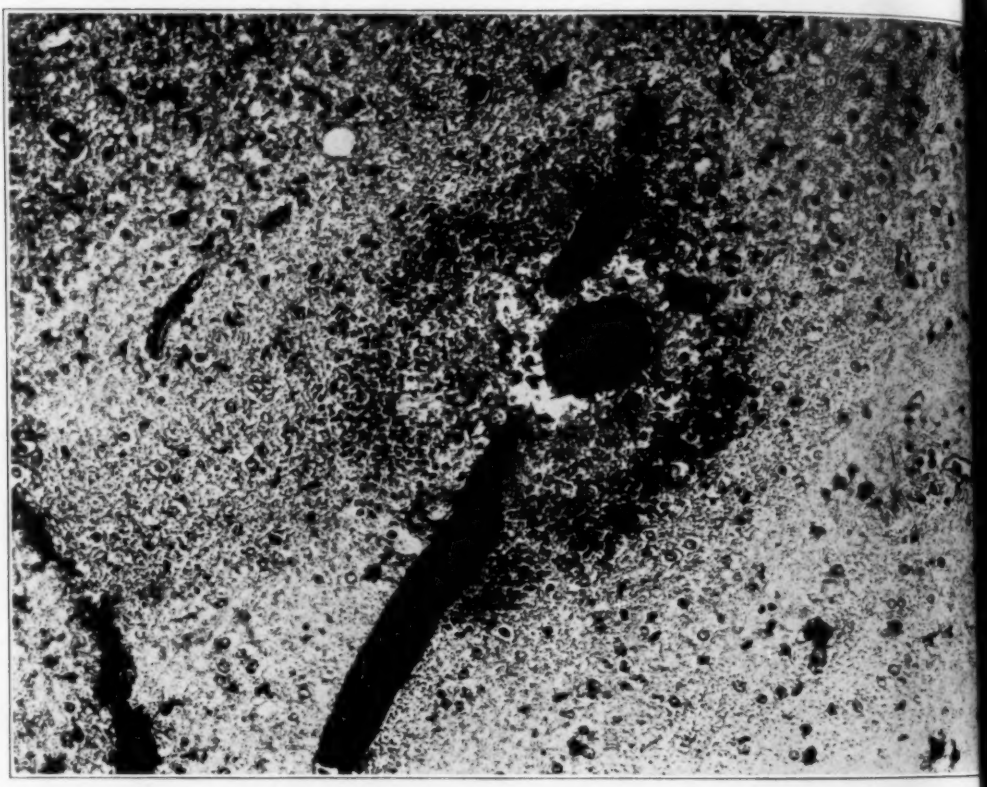

Fig. 3 (case 6).—Typical ring hemorrhage in brain, showing a fat embolus in an arteriole surrounded by a zone of necrotic brain tissue and red blood cells. Osmic acid stain.

These cases illustrate the difficulty of diagnosis whenever injuries to the head and fractures of the long bones are combined in the same patient. The fact that both patients were admitted to the hospital in coma and remained in coma as the result of the fractures of the skull obscured the typical clinical history of the cerebral fat embolism which developed later.

The absence of a patent foramen ovale or other communication between the right and left sides of the heart in case 7 is important in indicating that a systemic fat embolism can develop in the absence of any such opening.

Two cases described previously in a former report [58] illustrated the typical history of the cerebral fat embolism. One (case 8) was in a man, aged 25, who sustained a fracture of the right femur in an automobile

Fig. 4 (case 6).—Area of rarefaction in brain, with fat emboli in surrounding vessels. Osmic acid stain.

accident and lapsed gradually into coma about thirty hours after the injury. He died in coma six days and six hours following the trauma. In the other instance (case 9) a woman, aged 45, sustained a fracture of the right tibia and fibula in an automobile accident: two days later she lapsed into coma and died in coma four days later. In both cases petechial hemorrhages appeared on the skin of the upper part of the chest about the time that stupor developed, and they were still evident at the time of necropsy. Ring hemorrhages and areas of rarefaction were

present in the brain with numerous fat emboli in the vessels. These lesions showed the invasion of glial cells into the necrotic zones of brain tissue and attempts at repair (fig. 5). There were also fat emboli in the lungs, myocardium and kidneys which, however, were not obviously different from others already noted.

THE DIAGNOSIS AND TREATMENT OF FAT EMBOLISM

The majority of cases of fat embolism are so slight that they do not cause symptoms, or so severe that death results in a few days from

Fig. 5 (case 8).—Glial cells in an old ring hemorrhage. Hematoxylin and eosin stain.

involvement of the lungs or the brain. A few, however, have been reported in patients who after an injury gave a clinical picture of either the pulmonary or the cerebral form of this condition but who eventually recovered.

In two cases the diagnosis of pulmonary fat embolism was made. Field [71] described a case in which a patient who had suffered for several

71. Field, Merton: Fat Embolism from a Chronic Osteomyelitis, J. A. M. A. **59**:2065 (Dec. 7) 1912.

years from chronic osteomyelitis of the leg, one day inflicted an insignificant trauma on the diseased bone; after this a sudden attack of dyspnea developed and gross fat appeared in the urine. The patient recovered and the diagnosis of fat embolism was made from the clinical picture. In the case of Koch,[31] sterile human fat was injected into an old scar on the neck, and a few hours later the patient was seized with a severe but transient attack of shortness of breath. Koch attributed these symptoms to the fact that the fat was accidentally injected into a small vein and thus reached the blood vessels of the lungs. The diagnoses in both cases were probably correct, but of course there was no method by which they could be verified with certainty and the symptoms may have been due to other causes.

Other cases were described as examples of systemic fat embolism by Busse,[9] Bernhardt,[72] Wilms,[73] Benestadt [74] and Oppenheimer.[75] Each patient had sustained fractures of the long bones, and after an interval a slight stupor developed from which they recovered. In the cases of Busse [9] and Wilms [73] the diagnosis was made on these symptoms alone. Bernhardt [72] and Oppenheimer [75] claimed that they could detect the fat in the retinal arteries as ovoid globules, by use of the ophthalmoscope. The three cases of Benestadt [74] showed petechial hemorrhages in the skin of the shoulders and chest which gradually disappeared in a few days.

During life the diagnosis of fat embolism is justified only if there is a definite history of injury, and a characteristic clinical picture of either the pulmonary or the systemic type. Additional confirmatory signs are the presence of fat in the urine, the demonstration of fat emboli in the retinal vessels by the ophthalmoscope, and the appearance of the characteristic petechial hemorrhages in the skin of the upper part of the chest and shoulders. The discovery of large circular cells containing fat granules in the sputum, as noted by Elting and Martin,[56] and in the spinal fluid, as noted by Buerger,[63] is not a valuable diagnostic indication as the same changes can occur in other conditions than fat embolism.

As a rule, fat embolism is rarely diagnosed from clinical signs and symptoms; it is most often discovered accidentally at necropsy.

The differential diagnosis between cerebral fat embolism and intracranial hemorrhage complicating fracture of the skull has presented itself in one instance at least. As reported by Tobler,[76] a man, aged 64,

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72. Bernhardt, Friedrich: München. med. Wchnschr. **72**:1590 (Sept. 18) 1925.
73. Wilms: Semaine méd. **30**:138 (March 23) 1910.
74. Benestadt, George: Deutsche Ztschr. f. Chir. **112**:194 (Oct.) 1911.
75. Oppenheimer, H.: Klin. Wchnschr. **8**:24 (Jan. 1) 1929.
76. Tobler, J.: Schweiz. med. Wchnschr. **3**:452 (May 11) 1922.

was run over by a wagon and his right tibia fractured. On the second day after the accident he became stuporous and gradually lapsed into coma. A craniotomy was performed under the impression that he had a fracture of the skull with a complicating intracranial hemorrhage. No hemorrhage was found, and the patient died in deep coma on the fourth day after the trauma. Necropsy showed a marked cerebral fat embolism, but neither a fracture of the skull nor an intracranial hemorrhage.

It can readily be seen how the two conditions might be confused clinically under some circumstances. In a patient with a head injury and a fracture of a long bone of one of the extremities, a gradual lapse into coma might indicate an increasing intracranial hemorrhage, or a severe cerebral fat embolism. In typical cases the two would never be mistaken, as the intracranial hemorrhage is most often attended by signs of cerebral compression and definite neurologic signs referable to the site of the lesion. On the other hand, these syndromes are absent in cases of cerebral fat embolism, and lipuria, petechial hemorrhages of the upper part of the chest, and an ophthalmologic demonstration of the emboli in the retinal vessels may aid in establishing the diagnosis. Unfortunately, cases are not always typical, and often it is not possible to make the diagnosis during life.

The best treatment for fat embolism is to prevent its occurrence. In cases of fractures, effective immobilization of the broken bones is the most efficient means of lessening the absorption of the fat into the venous circulation. After the processes of repair have set in, the danger of this is past. In orthopedic cases, operations are performed by preference on patients whose marrow is cellular and not fatty, and an Esmarch bandage is used in an attempt to obviate the passage of an excessive amount of fat into the systemic veins from the operative site. Reiner [77] suggested that systematic tapping of the veins proximal to the fracture and distal to the Esmarch bandage would materially reduce the quantity of fat that reached the lungs, but there is no evidence that this method is at all effective.

Other therapeutic measures advised by different investigators are not of much practical value. The idea of Wegelin,[55] that an intravenous injection of sodium carbonate hastens removal of the emboli by saponification, does not promise to be effective. The theory of Wilms,[73] that drainage of the thoracic duct lessens the amount of fat embolism in the pulmonary vessels, is based on the false conception that fat is transported from the site of injury by the lymphatic vessels. As a therapeutic procedure it would be practically useless.

As a rule, when the fat has entered the blood stream, the result must be left to the natural defenses of the body and only symptomatic treatment can be applied.

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77. Reiner: München. med. Wchnschr. **54**:2004 (Oct. 1) 1907.

FAT EMBOLISM IN ANIMAL EXPERIMENTS

Much of the information concerning fat embolism has been acquired through experiments on animals, so that in order to gain an adequate conception of the subject it is necessary to review briefly the work in this field.

The early experiments were concerned mainly with the discovery that a viscous oil, like olive oil, when injected into the vein of an animal, produced death in a few minutes from asphyxia and edema of the lungs. Majendie [78] recorded the results of such an investigation about 1832. Over twenty years later Virchow [79] repeated the same experiment and in addition demonstrated typical fat emboli in the pulmonary arterioles and capillaries, which he believed were responsible for the death of the animal.

Busch [3] contributed an important addition to the general knowledge of the subject when he demonstrated that injuries to the adipose tissue in the skeleton resulted in a definite fat embolism in the lungs. He made a trephine opening in the tibia of a rabbit, traumatized the fatty marrow of the shaft with a sound and produced characteristic fat emboli in the pulmonary vessels. He also showed that if olive oil colored by cinnabar was injected through such a trephine opening into the medullary cavity of the tibia, three significant phenomena were noted: 1. The haversian canals of the bone into which the injection was made were stained heavily by the cinnabar, indicating that the colored olive oil had been absorbed into the haversian veins. 2. Numerous cinnabar-colored fat emboli were found in the lungs; this was additional evidence that they were derived from the fat in the bone marrow. 3. If the inferior vena cava was canalized just prior to the injection, cinnabar-stained oil globules would flow from the canalized vein immediately after the injection; this pointed to the fact that the absorption of the fat from the bone was rapid and that its transportation to the lungs was swift.

Much more recently the experiments of Fritzsche,[80] Schultze,[12] and Caldwell and Huber [81] furnished additional verification that fat is rapidly absorbed from a fracture of the shafts of the long bones. Schultze fractured the tibia of his animals and then canalized the main venous trunk of that extremity. The primary fracture caused only a few droplets of fat to pass through the cannula, but any further trauma to the area of injury, such as light blows, movement of the bones or a sudden ecchymosis in the affected part, caused a large number of oil

78. Majendie, quoted by Scriba (footnote 43).

79. Virchow, Rudolph: Virchows Arch. f. path. Anat. **5**:308, 1853.

80. Fritzsche, E.: Deutsche Ztschr. f. Chir. **107**:456, 1910.

81. Caldwell, George T., and Huber, Harry L.: Surg. Gynec. Obst. **25**:650 (Dec.) 1917.

globules to enter the vein. He believed that the natural aspirating force of the torn haversian veins allowed the fat to gain entrance to the circulation, and that a rise of pressure in the area of fracture from hemorrhage, muscular spasms and the like would serve to increase the amount of fat absorbed to a dangerous degree. His experiments confirmed and supplemented the observations of Siegmund [5] and Sutton [6] on clinical cases.

Caldwell and Huber [81] also produced pulmonary fat embolism by fracturing the tibia of rabbits. They claimed that if an Esmarch bandage was bound around the extremity proximal to the fracture and retained in position for two hours, the number of the emboli in the lungs would be much less than if the Esmarch bandage was not used. These observers explained their results by the fact that the two hour application of the bandage prevented a large absorption of fat until the processes of repair had closed the ruptured veins at the site of fracture.

The experiment of Ribbert [82] seemed to indicate that fat embolism could be produced by trauma to the skeleton without actual fracture of the bones. He anesthetized a rabbit, struck the shaft of the tibia repeated light blows with a rod and later demonstrated fat emboli in the lungs. He did not describe any lesions in the bones or bone marrow, but attributed his results to the jarring force that he inflicted on the bone with the rod. Fritzsche [80] and Schultze [12] duplicated this experiment, and considered that the emboli could be caused in this manner. In fact, Fritzsche claimed that a slight grade of fat embolism is found normally in rabbits because of the propensity of the animals to thrash around in their cages. Similarly, McKibben [83] described fat embolism in normal cats. Schultze offered the explanation that the jarring of the bones tears small veins and ruptures small groups of fat cells at their attachment to the firm bony trabeculae, with the production of numerous minute hemorrhages in the bone marrow and a consequent rise of intra-osseous pressure. The mechanism for absorption of fat into the blood is thus provided and an embolism results.

A few investigators have believed that a lipemic condition of the blood can be a potent etiologic factor in the production of fat embolism. In lipemia, such as occurs during digestion, fat is present in the blood in the form of an emulsion so finely divided that it passes readily through the finer capillaries and, under normal conditions, rarely coalesces into globules large enough to cause vascular obstruction. Wuttig [84] claimed, however, that he produced pulmonary fat emboli in rabbits by causing lipemia from the excessive ingestion of cod liver oil. Similarly,

82. Ribbert (footnote 10, first reference).

83. McKibben, P. S.: Am. J. Physiol. **48**:331 (April) 1919.

84. Wuttig, H.: Zieglers Beitr. z. path. Anat. **37**:378, 1905.

Lehman and Moore [85] produced lipemia in dogs by feeding them cream, and then gave the animals ether, either intravenously or by inhalation. On postmortem examination fat emboli were found in the lungs in considerable numbers, while control animals whose blood was not lipemic did not show analogous changes. They believed that the ether acted as a deemulsifying agent by precipitating fat from the blood serum in globules large enough to plug the vessels.

Markowitz and Mann,[86] in their experiments on dogs, claimed that they produced histologic pictures resembling fat embolism in the lungs by the intravenous injection of finely divided fat emulsions. No explanation was given for the precipitation of the fat from this emulsified form into the larger globules in the blood.

At present it is too early to speak with any authority on the possibility of fat emboli arising from lipemia, but it is not probable that this condition is an important etiologic factor in human beings.

The transportation of the liquid fat from the site of injury to the pulmonary arterioles and capillaries is primarily through the venous circulation by the direct route, as the experiments of Busch [3] and Schultze [12] have indicated. Some investigators, among whom are Busch, Wiener,[87] Riedel [88] and Fritzsche [80] have suggested that some of the fat is absorbed by torn lymphatic vessels and carried to the thoracic duct and eventually discharged into the venous circulation. After a lapse of twenty-four hours, a severe pulmonary fat embolism will be caused, according to Fritzsche. This investigator claimed that in his experiments on rabbits and dogs, ligation of the venous trunks draining the extremity on which a fracture had been inflicted could not keep the emboli from the pulmonary vessels, but that ligation of the thoracic duct inhibited their occurrence. Fritzsche's theory was that fat so absorbed had the power to pass unchanged through the lymph nodes in its route to the thoracic duct.

In recent years, the evidence is that very little fat is absorbed by the lymphatics at the site of injury, and that it is subjected to lytic changes in its progress through the adjacent lymph nodes. The experiments recorded by Wegelin [65] showed that olive oil injected into rabbits subcutaneously, intrapleurally and intraperitoneally gives rise to a few emboli in the lungs, and that most of the oil is found in the nearest lymph nodes in a state of saponification. According to Wegelin, the lymphatic tissues are strongly lipolytic, and fat is not likely to pass through them intact. In any event, it is dubious that liquid fat in

85. Lehman, E. P., and Moore, R. M.: Fat Embolism Including Experimental Production Without Trauma, Arch. Surg. **14**:621 (March) 1927.

86. Markowitz, Cecile; and Mann, F. C.: Am. J. Physiol. **73**:521 (June) 1930.

87. Wiener, M.: Arch. f. exper. Path. u. Pharmacol. **11**:275 (Sept. 3) 1879.

88. Riedel, B.: Deutsche Ztschr. f. Chir. **8**:571, 1877.

appreciable amount is conveyed from the injured area by the lymphatic vessels, and it is certain that the venous circulation is the only important channel in the production of the pulmonary form of embolism.

In its passage through the pulmonary arteries or other vessels the fat tends to break up into smaller and smaller globules as the emboli reach the finer and finer ramifications. As Fuchsig [89] noted in a fat embolism induced in the mesentery of the frog, the emboli divide into smaller globules which enter the capillary network in single file. Investigation of the lungs microscopically suggests that some such process takes place here. Apparently the distribution of the fat throughout the lungs is uniform for the most part. The theory of Kretz [90] that fat emboli entering the blood through tributaries of the superior vena cava involve mainly the upper lobes and that emboli entering in tributaries of the inferior vena cava involve mostly the lower lobes is not considered tenable. Wegelin [55] noted that in any one case of fat embolism all parts of the lungs show practically the same proportion of emboli.

The effect of fat embolism on the organism has been the subject of much experimental study. It is evident from the results recorded that many factors influence the reaction of the animal to the injected mass. If it is given rapidly in large amounts into the juguiar vein, as was recorded in the experiments of Virchow,[79] death occurs in a few minutes from asphyxia. If, however, the oil is injected slowly into a smaller venous trunk, larger quantities can be given before the animal shows signs of respiratory distress, as Wegelin mentioned. Paul and Windholz [65] declared that by injecting large intravenous doses of oil in carefully graduated amounts at selected intervals they were able to create a tolerance for fat embolism in their animals. One that had been carefully prepared in this fashion could withstand comfortably the injection of an amount of oil sufficient to cause the death of an animal not similarly treated.

One effect of oil injected intravenously is to lower blood pressure, as was made manifest in the work of Simonds,[91] Wiggers [92] and Porter.[93] The widespread embolism obstructs the passage of blood through the pulmonary circulation into the systemic circulation, reduces the volume of fluid in the arterial trunks, and seriously interferes with the strength of the heart beat because of the interference with oxygenation in the pulmonary vessels. The arterial pressure conse-

89. Fuchsig, Ernst: Ztschr. f. exper. Path. u. Therap. **7**:702, 1910.

90. Kretz, quoted by Wegelin (footnote 55).

91. Simonds, J. P.: A Study of Low Blood Pressures Associated with Peptone Shock and Experimental Fat Embolism, J. A. M. A. **69**:883 (Sept. 15) 1917; J. Exper. Med. **27**:539 (May 1) 1918.

92. Wiggers, Carl B.: Circulatory Failure, J. A. M. A. **70**:508 (Feb. 23) 1918.

93. Porter, W. T.: Boston M. & S. J. **180**:531 (May 8) 1919.

quently decreases in a manner suggestive of shock induced by trauma. In fact, the similarity between the two conditions in this respect inspired the three investigators mentioned to see what connection might exist between traumatic shock and fat embolism.

As described by Cannon,[94] traumatic shock occurs shortly after severe wounds and is manifested by a general collapse of the organism, with lowered blood pressure, a rapid weak pulse and respirations, a low temperature, increased viscosity of the blood, signs of acidosis and similar symptoms, often severe enough to result in death. All these symptoms are referable to a stagnation and retention of the blood in the capillary bed of the body and an inability of the circulatory mechanism to force the blood properly through the vessels and oxygenate it sufficiently. The end-result is therefore a deficient interchange of oxygen, not only in the lungs but also in various organs elsewhere, with consequent damage to the injured person. It is evident that traumatic shock is composed of a number of different phenomena and that the knowledge of its etiology is as yet incomplete. From the results of observations and experiments, it seems probable that shock is a condition totally distinct from fat embolism, but that in occasional instances many of the symptoms referable to shock may be the result of an association with the latter condition.

The experiments of Gold and Loeffler [57] indicated the effects of an artificially induced fat embolism on an artificially induced traumatic shock in cats. Their cats were separated into two series: (1) normal animals used as controls, and (2) cats in which shock was produced either by traumatizing the intestines or by compressing the inferior vena cava near the liver. Liquid fat was injected intravenously into both series of animals. The control animals showed merely signs of a pulmonary fat embolism, with asphyxia, dyspnea and a slight decrease in blood pressure. The cats shocked by trauma exhibited a low blood pressure before the injection of oil, but if kept undisturbed usually returned to a normal state. The intravenous injection of oil in an amount that would scarcely affect a control animal had a deleterious effect on the shocked animal, for the blood pressure remained low and the symptoms of shock were unduly prolonged. Gold and Loeffler believed that fat embolism was distinct from traumatic shock but that it often occurred in association with the latter condition and merely enhanced the symptoms of vascular collapse already present.

The experiments of Scriba,[43] Reuter,[95] Kojo,[96] and Paul and Windholz [65] proved that fat injected into a systemic vein could pass through

94. Cannon, W. B.: A Consideration of the Nature of Wound Shock, J. A. M. A. **70**:611 (March 2) 1918.

95. Reuter, Wolfgang: Frankfurt. Ztschr. f. Path. **17**:205, 1915.

96. Kojo, quoted by Wegelin (footnote 55).

the pulmonary capillaries into the arterial circulation and be distributed to the different organs. A large portion of the emboli centered themselves in the brain. Scriba [43] was of the opinion that the lesions in the brain alone could produce sudden death. Fuchsig [89] and Porter [93] observed a case in which rapidly fatal collapse occurred when an artificial fat embolism of the medulla was produced. The latter was prone to attribute the lethal cases of wound shock to this condition. Others, including Reuter,[95] believed, on the contrary, that fat emboli cause comparatively little damage to the central nervous system. Reuter claimed that in his experiments olive oil injected into the carotid arteries of a rabbit passed the cerebral capillaries as well as the pulmonary capillaries, and eventually was found in the lungs. He regarded the lungs as a natural filter of liquid fat from the blood, and as capable of harboring large numbers of emboli without difficulty.

It was believed for a long time that liquid fat could be forced through the pulmonary capillaries into the arterial circulation and from the systemic capillaries back into the venous circulation. The process could be repeated until finally the fat was absorbed from the blood; the name given to it was cyclic fat embolism. It is possible that this condition has been approximated in animal experiments for, as Wegelin [55] pointed out, different oils have different viscosities; olive oil, for instance, is much less viscous than human fat and therefore more capable of passing through the capillaries. It is difficult to conceive, however, of any cyclic phenomena of this kind occurring in human pathology, especially in the fat embolism induced by trauma.

In recent years many oils of low viscosity have been given intravenously as a therapeutic measure. The use of chaulmoogra oil in leprosy is well known and it apparently can be given in this manner without ill effects. Fischer,[45] Leo [97] and Lepehne [98] experimented with intravenous injections of eucalyptol-menthol as an antiseptic agent in pulmonary tuberculosis and of camphor as a circulatory stimulant, but the solutions that they used appear to be irritative apart from whatever ill effects they may cause in the rôle of fat emboli.

Fat emboli have a definite action on the systemic organs and cause the lesions that have already been described. Recently the effect of the embolism on the blood chemistry of animals was studied by Paul and Windholz [65] and by Flick and Traum.[66] Paul and Windholz produced a nitrogen retention of a uremic type, and a marked hypoglycemia in the blood of rabbits by the intravenous injection of liquid human fat. They attributed these results to a widespread fat embolism of the kidney and liver, respectively. In addition, the same investigators

97. Leo, H.: Deutsche med. Wchnschr. **48**:155 (Feb. 2) 1922.
98. Lepehne: Klin. Wchnschr. **1**:670 (April 1) 1922.

described deposits of pigment in the spleen and fatty changes in the liver which they considered due to hemolytic and toxic products produced by saponification of the emboli.

Flick and Traum,[66] in a similar manner, injected dog fat intravenously into normal dogs and demonstrated that a nitrogen retention followed the embolism.

Schultze [12] suggested that in many instances fat absorbed from the fracture of a leg bone becomes adherent to the wall of the femoral vein and later undergoes saponification so that the intimal layer is irritated. A reactive inflammation is induced, and a bland thrombus may form in the vein. Just how far this process operates in thrombosis of the femoral veins following a fracture or other injury to the lower extremity is not well understood.

The elimination of fat emboli from the system has been estimated as occurring in from eight to fourteen days, according to Reuter.[93] Gauss [1] listed four ways in which the intravascular fat can be removed from the body: (1) excretion by the kidney, (2) disposal by the liver, (3) removal by phagocytic endothelial cells and (4) solution of the embolus by a lipase either in the blood or in the tissues.

The elimination of the fat by the kidney has already been discussed. As far as the liver is concerned, the experiment of Wuttig [84] showed that the parenchyma cells and Kupffer cells in the immediate vicinity of the embolus are filled with fat droplets. He believed that the organ has the power of absorbing the fat from the blood vessels. It is probable, however, that phagocytosis by endothelial cells, as noted by Beneke [99] and others, and saponification by lipases, as mentioned by Paul and Windholz [65] and by Wegelin,[55] are the two most important methods of removing the intravascular fat.

Lehman and McNattin [100] described this phagocytic process around the experimental fat emboli in the lungs of dogs that had received intravenous injections of cotton seed oil. At first, large endothelial and giant cells appeared around the fatty plug, and later areas of pneumonia and scar tissue nodules developed as an after-effect of the embolism.

Similar pictures have not been described in the experimental fat embolism of other organs, aside from a brief mention by Paul and Windholz of small glial scars in the brains of animals.

COMMENT AND SUMMARY

It is obvious that fat emboli frequently occur after trauma to fatty tissue, especially in the shafts of the long bones. In the majority of

99. Beneke, R.: Zieglers Beitr. z. path. Anat. **22**:343, 1897.

100. Lehman, E. P., and McNattin, R. F.: South. M. J. **22**:201 (March) 1929.

cases the grade of embolism is slight, indicating that the protective mechanisms of the organism work with sufficient efficiency to prevent the absorption of fat into the blood stream in any considerable amount. Severe and fatal cases of fat embolism are exceptional. Table 2, in which fifty-nine cases of fractures of the bones of the extremities are analyzed, shows about 75 per cent positive for fat emboli and 25 per cent negative. Only three cases, or approximately 5 per cent of the total number belonged to the fatal group.

An analysis of the material indicated that fat emboli could be demonstrated in the pulmonary arterioles a few minutes after a fracture. The transportation from the site of injury to the lungs was rapid. The emboli could be found rather consistently in the lungs during the first seven days after the trauma, but were discovered only occasionally after that period, as they were probably being removed from the circulation. The sections of the lungs and other organs were searched for evidences of phagocytosis or other signs of removal of the emboli; however, aside from finding large spherical cells with fatty granules near the impacted globule, the results were negative. As these same cells were occasionally present in toxic conditions not associated with fat embolism, little significance was attached to their appearance.

The positive results in the series of nontraumatic cases were only to be interpreted as an indication that in some way a small amount of fat had gained entrance to the circulation and formed emboli in the lungs. Probable explanations were that adipose tissue somewhere in the body had been slightly damaged from a convulsion or a fall, or that some oily substance like camphor had been injected into a subcutaneous vein by accident. In any event, the degree of the process was slight and not of any importance clinically or pathologically. Its chief significance lies in the implication that a slight grade of pulmonary fat embolism cannot be used as a positive confirmatory sign of trauma. Given a fracture of a bone in the leg in a person found dead under suspicious circumstances, unless other signs indicated that the violence was inflicted during life, a few fat emboli in the lungs would be useless as a criterion of intravital injury.

On the contrary, a severe grade of fat embolism, especially when some of the emboli have been forced from the pulmonary into the systemic circulation, is a reliable indication of intravital trauma, if a definite injury is present and if one can exclude the only other cause, the intravenous injection of an oily liquid in large amounts. As this last process is uncommon in human pathology, it can be ignored as a practical consideration.

Other alleged causes, such as burns, poisons, postmortem processes and lipemic conditions due to natural causes, are associated only with slight grades of fat embolism, and are not important.

It is also certain that severe fat embolism gives rise to two distinct clinical pictures associated with definite pathologic lesions: 1. The pulmonary type, which occurs in the first two days after the injury, is referable to a marked obstruction of the arterioles and capillaries of the lungs. The patients die as the result of asphyxial symptoms. 2. The emboli may pass through the pulmonary capillaries into the systemic circulation, and cause definite lesions in the brain, heart and other organs. In such instances, death occurs in from two to seven days from the involvement of the central nervous system; for this reason, this type is known as the cerebral type.

The clinical diagnosis of fat embolism is made only occasionally because the complication is rare and because the symptoms may be attributed to some other condition in the body. The asphyxial symptoms of the pulmonary form may be confused with the terminal symptoms of an associated chronic disease of the heart and lungs. This may occur all the more readily because a pulmonary embolism of moderate grade can aggravate lesions of this type.

The cerebral type is often overlooked, especially if an injury of the head is present, as the coma from the latter not only may obscure the typical clinical picture but, on occasion, may simulate it. This was seen in the case reported by Tobler,[70] in which the patient's lapse into unconsciousness was attributed to cerebral compression referable to a supposed epidural hemorrhage rather than to the widespread cerebral fat embolism that was actually present.

The diagnosis during life is not easy and can be made only if the possibility of fat embolism is kept in mind, and if the symptoms and signs that suggest it are not overlooked. For this purpose, hard and fast rules cannot be formulated, but much must be left to the native astuteness of the individual diagnostician.

NORMAL AND PATHOLOGIC REPAIR IN THE THYROID GLAND*

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In the large accumulation of studies referable to the thyroid gland, the vast majority are concerned chiefly with pathologic states, the most common being goiter with its various types and classifications. And yet not all goiters represent pathologic conditions. An enlargement of the thyroid gland is not an unusual event in the life of a person, especially in certain regions, and it often represents a physiologic response of the organ to certain stimuli. This gross change in the size of the gland is often associated with both chemical and microscopic changes. That increase in the activity of the thyroid gland is associated with an increase in the metabolism of the body is such a well known fact that it requires but little comment. This has been shown not only by an increase in the body's excretion of nitrogen, but by an increase in the consumption of oxygen. So definite is this that the level of the basal metabolism is often used as an index of thyroid activity. The cellular change seen in the gland may be both marked and varied. It may consist merely of a change in the size and shape of the cells with an increase in the mitochondria, or it may be so extensive, owing to hyperplasia and desquamation of the parenchyma, that the normal architecture of the gland may be lost. The cytology of the gland with special reference to the mitochondrial changes has been carefully studied by Key.[1]

So far as is known at present, the stimuli that produce a demand for an increase in the function of the thyroid gland are numerous. Physiologically, such a demand occurs during puberty and adolescence, at menstrual time and during pregnancy. Certain dietary deficiences have a marked effect, as has been shown by McCarrison.[2] Webster and Chesney[3] have produced goiter in rabbits by feeding cabbage. Some

* Submitted for publication, Dec. 11, 1930.

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1. Key, J. A.: The Secretion Antecedents and Mitochondria in Pathologic Thyroids, Arch. Surg. **11**:254 (Aug.) 1925.

2. McCarrison, Robert: The Simple Goitres, New York, William Wood & Company, 1928.

3. Webster, B., and Chesney, A. M.: Studies in Etiology of Simple Goitre, Am. J. Path. **6**:275 (May) 1930.

time ago we[4] showed that various types of infections and toxemias could produce these changes. More recently we demonstrated that hyperactivity of the gland could be caused by the injection of certain drugs, notably the methylated purines and related substances.[5] Accordingly, we feel that various degrees of hypertrophy and hyperplasia of the thyroid gland with subsequent involution are extremely common. There are perhaps few organs in the animal body subject to more frequent and greater anatomic changes due to a transient increase in function than is the thyroid. These changes may take place in a comparatively short period of time. We have observed a marked transformation in as short an interval as eighteen hours. It may be in the form of an intense desquamation of epithelium and loss of colloid, so that the thyroid may be difficult to recognize as such microscopically, or if the stimulus is not so great the changes will not be so great and will be those of hyperplasia instead. If the stimulus is milder still, one sees acini with columnar cells, vascular congestion and thin, poorly staining colloid along with other evidences of increased activity of the thyroid gland. When a slight increase in activity is demanded over a long period of time, the changes frequently produced resemble, perhaps more than any other, those of exophthalmic hyperplasia. Apparently the amount of change produced in the gland depends on the strength of the stimulus and the time it is at work and the amount of colloid or iodine that is present in the thyroid or that is easily available. Intense changes in the thyroid gland occurring during an infection can be almost completely prevented by feeding the animal large doses of iodine. Likewise, we have found it more difficult to produce glandular changes in the summer when the thyroid is in a more complete resting phase and thus contains more iodine.

Since it is possible to produce hyperplastic changes in the thyroid gland experimentally, and since it is likewise possible to cause an artificial involution by the use of iodine or a natural involution by the withdrawal of the stimulus, it occurred to us that it would be of value to study the anatomic changes that occur in the gland by a repetition of this cycle.

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4. Cole, W. H., and Womack, N. A.: Reaction of the Thyroid Gland to Infections in Other Parts of the Body, J. A. M. A. **92**:453 (Feb. 9) 1929. Cole, W. H.; Womack, N. A., and Gray, S. H.: The Thyroid Gland in Infections and Toxemias: Pathological Changes in the Human Gland, Am. J. Surg. **6**:221, 1929. Womack, N. A.; Cole, W. H., and Heideman, A. G.: The Thyroid Gland in Infections: The Effect Upon the Basal Metabolic Rate, Endocrinology **12**:733, 1928.

5. Cole, W. H.; Womack, N. A., and Ellett, W. H.: The Production of Hyperplasia of the Thyroid Gland by Chemical Means, Arch. Surg. **22**:926 (June) 1931.

METHODS AND MATERIALS

We used dogs in this experiment because of their accessibility, the size of the thyroid in this animal and the fact that excess scarring in the gland of a normal dog is unusual. Although tumors do occasionally occur in dogs, in the vicinity of St. Louis they are usually definitely neoplastic in type. As a control, the gland of each animal was inspected before the experiment was begun, and a small section was removed from the inferior pole of the right lobe for microscopic study. Those animals were discarded in which glands were not in the resting phase. The picture (fig. 7*A*) of a thyroid gland without nodules, visible scarring and in a resting phase we took as normal.

The amount of connective tissue in such a gland is noticeably less than that in the gland of an adult human being. The gland is surrounded by a rather thin capsule of areolar and fibrous connective tissue from which small trabeculae arise and extend centrally. The gland is rarely divided into lobules, as is often seen in man, for usually the connective tissue is difficult to demonstrate except in the proximity of the capsule and around larger blood vessels. It is generally stated, however, that a delicate reticulum of connective tissue extends along the smaller capillaries surrounding each follicle and forms a stroma for the gland. We were unable to demonstrate such a reticulum of connective tissue completely, even with the use of special stains. However, it is an extremely delicate network. By the use of the van Gieson and Mallory stains, Key [1] was able to demonstrate such a reticulum in human glands. The location of this fibrous tissue is important for, as we shall attempt to show, an increase in connective tissue is often associated with considerable anatomic distortion of the gland.

Hyperplasia of the thyroid was produced by the production of infections, the injection of drugs, chiefly methylated purines, and the implantation of contaminated foreign bodies over a long period of time. It is interesting to note that every acinus is not affected to the same degree during the production of hyperplasia. In one area one may see overwork to the point of cellular death while in an area closely adjoining there may be only a mild amount of increased activity on the part of the cells.

REPAIR

Apparently the thyroid gland has a remarkable power of regeneration similar to that of parenchymatous organs such as the liver and the kidney. Cells that are injured beyond repair are desquamated into the lumen of the acinus and are speedily replaced by newly formed thyroid cells. Figure 1 illustrates this method of repair. It is interesting to note that within five days after fairly extensive injury an excess amount of regeneration takes place and these new cells in turn are hyperactive. This is probably the most common type of repair, and, as it is associated with little injury to the connective tissue or vascular injury, fibrosis is not a notable feature.

When an entire acinus is destroyed, it is doubtful whether this is replaced. Compensatory hyperplasia probably takes place in the remaining acini. A counterpart to this is seen in the liver, when an entire lobule is destroyed, and in the kidney, when an entire tubule is injured; collapse of the supporting reticulum occurs. When

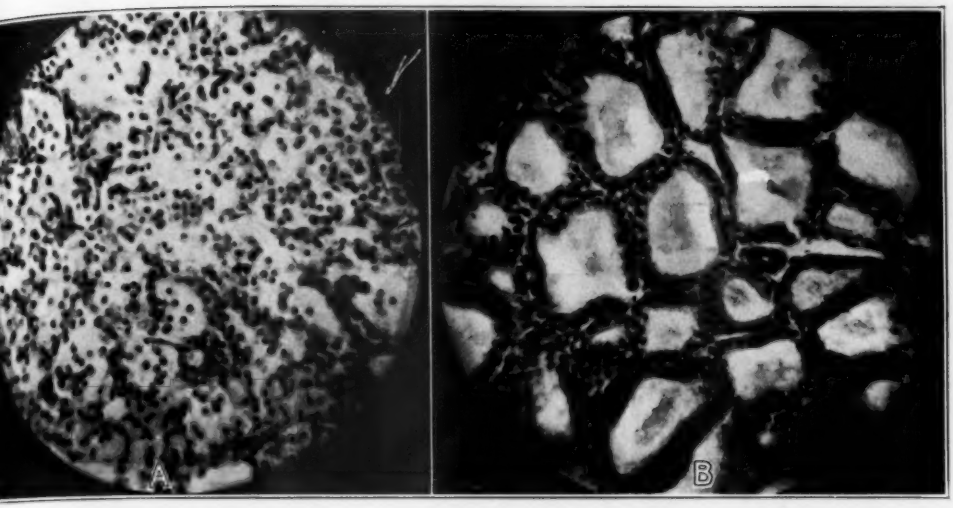

Fig. 1.—*A*, section taken from the thyroid gland of a dog with a severe infection of the leg. Note the loss of colloid and the desquamation of the cells into the lumen of the acinus. In most of the acini some of the epithelial cells still remain intact. *B*, section taken from the same dog five days later. The infection in the leg has largely subsided. Here one sees complete regeneration of the acinar cells with little or no scarring. The cells are columnar in type and show hyperplasia in several areas. Colloid is beginning to reappear.

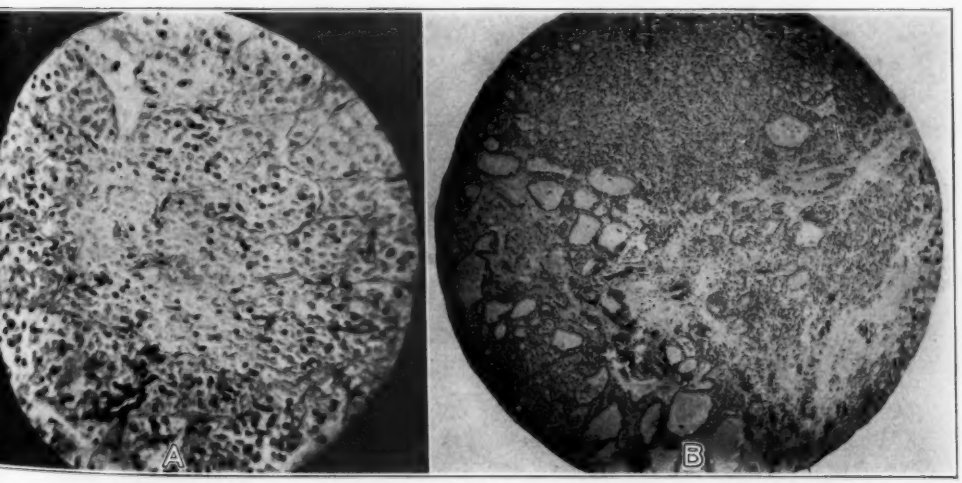

Fig. 2.—*A*, massive necrosis of the thyroid following administration of a large dose of caffeine alkaloid by mouth (0.15 Gm. per kilogram). Note the destruction of the entire acini. *B*, replacement of localized fibrous tissue in the thyroid of a dog following a severe infection.

injury is so severe, there is usually a varying degree of damage to the underlying stroma. This results in fibroblastic proliferation and, like such proliferation elsewhere, it is usually excessive. Figure 2*A* shows such an area of complete necrosis following a toxic dose of caffeine. Figure 2 *B* shows the probable type of replacement of fibrous tissue that follows such a focal injury.

We found it difficult to produce the extensive diffuse perilobular fibrosis that is so commonly seen in the human gland following treatment

Fig. 3.—Encapsulated nodule involving the upper pole of the thyroid gland of a dog one month after laparotomy and a localized peritonitis. Previous examination of the gland had shown no nodules.

with iodine therapy in exophthalmic hyperplasia. This may be due to the scant amount of connective tissue occurring between the acini in the dog, as was mentioned in the early part of this paper. Consequently we did not produce the multinodular goiter that one often encounters. Certainly in our cases, most of the fibrosis seemed to emanate from those regions near larger blood vessels where connective tissue was normally more profuse. We were able to demonstrate fibrosis in scattered areas

and likewise we were able to demonstrate small so-called adenomas. The mechanism of the production of these nodules is probably the encircling of a group of acini by fibrous tissue with subsequent cycles of hyperplasia and involution. Figures 3, 4 and 5 show the formation of nodules encapsulated and similar in every respect to their counterpart in the human gland. The formation of these nodules was apparently in proportion to the amount of fibrosis in the gland. By producing a profuse ingrowth of fibrous tissue by means of the injection of a trypsin

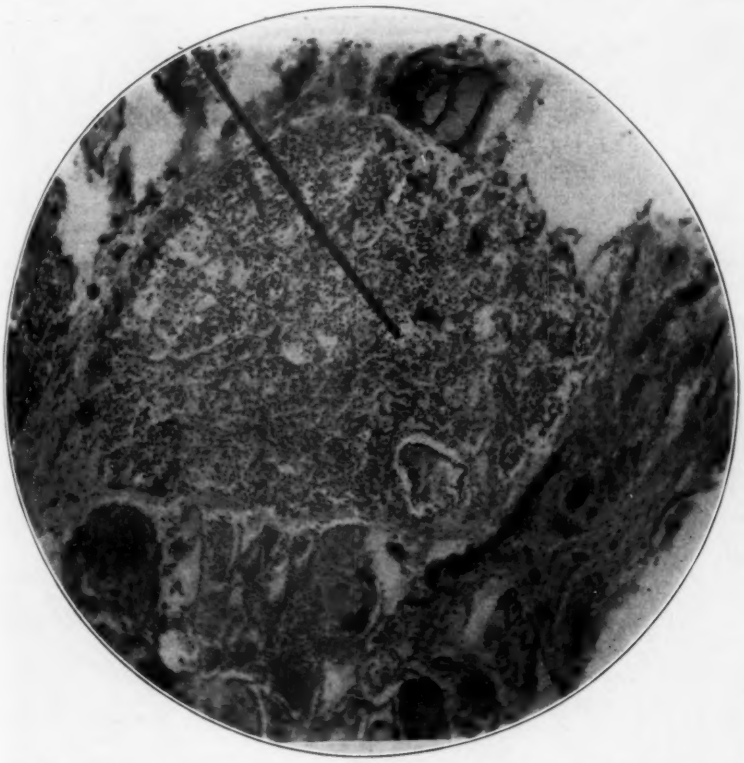

Fig. 4.—Section taken from the thyroid gland of a dog nineteen days after the injection of a solution of trypsin into the inferior thyroid arteries. There was a diffuse fibrosis throughout the gland. In this section one sees an "adenoma" formed by a group of acinar cells being cut off and surrounded by connective tissues. A previous section of the gland was normal. Inspection of the entire gland at that time showed no nodules.

solution into the inferior thyroid artery or by other methods, we noted nodular changes much more frequently. Some of these nodules resembled the so-called fetal adenoma in such detail that while we cannot disprove the theory of embryonic rest, we are inclined at the present

time to explain the presence of these nodules on the basis of morphologic changes as a result of a natural physiologic cycle. Although we have no proof that these adenomas were not already present in a microscopic form before our experiments were started, we wish to emphasize the fact that in sections taken from several hundred normal dogs in the past few years, we did not encounter a single instance of an adenoma.

We have shown in previous studies that iodine protects the animal to a large extent from these hyperplastic changes in the thyroid. Natu-

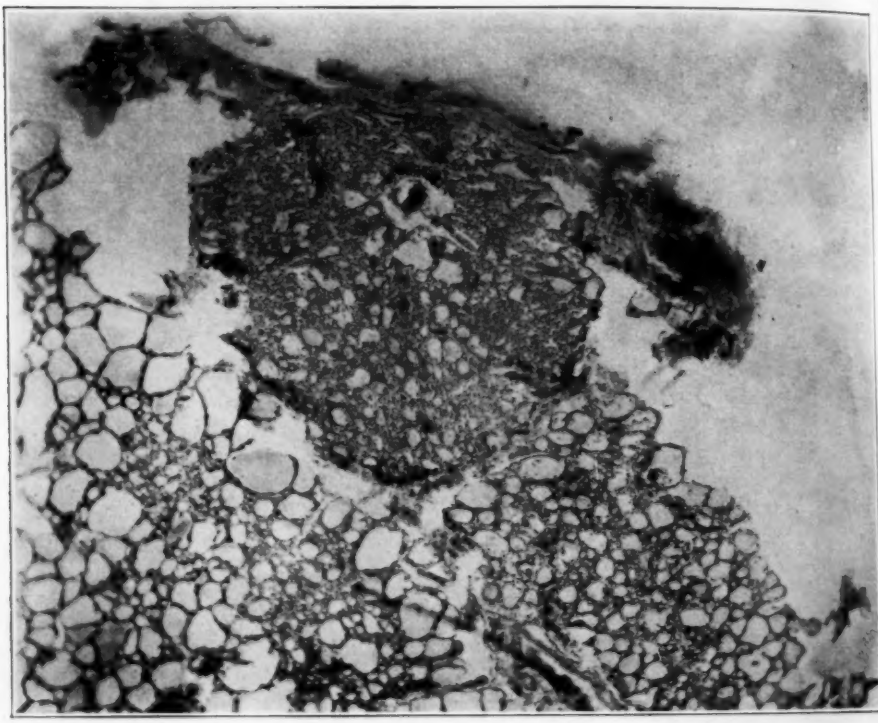

Fig. 5.—Nodule in the thyroid gland of a dog dying five days after the administration of a compound solution of iodine. This dog was emaciated, had a fever of 104 F., and was very ill when received. It no doubt was suffering from an infection of long duration. Gross examination at the time of the autopsy did not reveal the cause of death. There was no previous biopsy done on this animal.

rally, in such cases fibrosis does not occur (fig. 6). However, if the hyperplastic changes have been present for several weeks and the animal is then fed iodine, a certain amount of replacement of fibrous tissue takes place in spite of the fact that parenchymatous regression may be such that it is difficult to differentiate from the former sections of the

same gland in its resting phase. If the iodine is again withdrawn, hyperplasia will reappear and will persist until sufficient iodine is again given the animal or until the stimulus causing the change is withdrawn. Figure 7 shows such a train of events. Note the similarity of the final photographs to the structure of the thyroid in exophthalmic goiter.

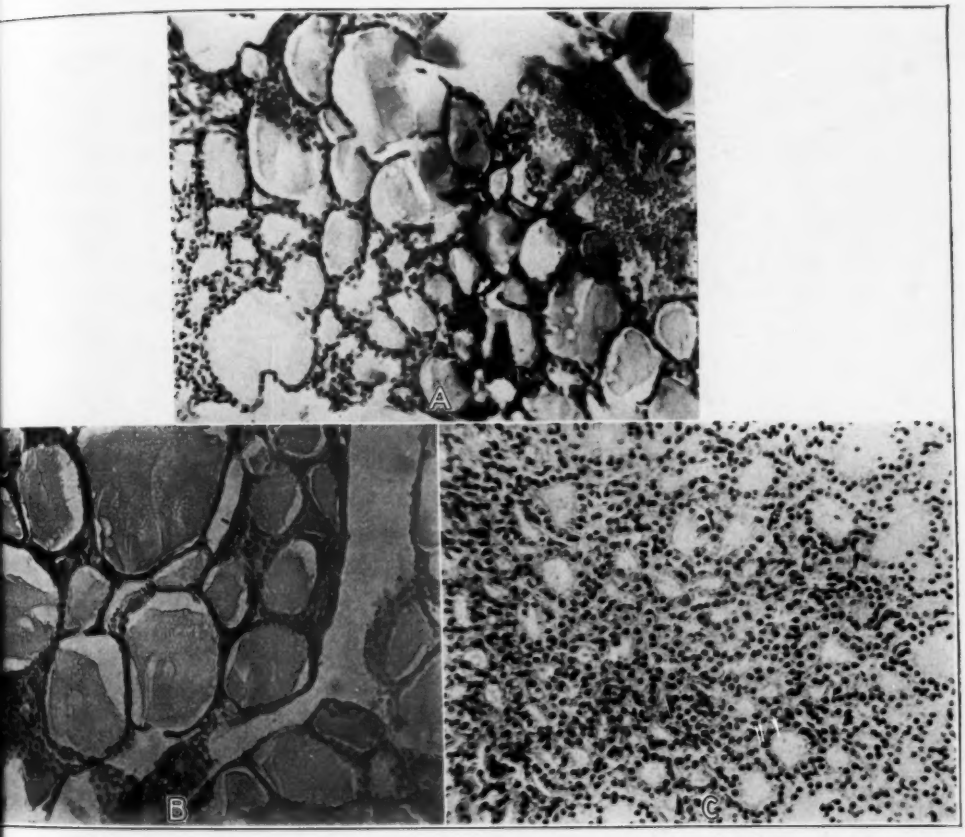

Fig. 6.—*A*, normal control section taken from the thyroid gland of a dog, after which a contaminated foreign body was buried in the muscles of the neck. The animal was then given a compound solution of iodine. *B*, section from the thyroid of the same dog after two weeks of administration of a compound solution of iodine. The gland shows no great amount of change, owing, we think, to protection offered by the iodine. Note the absence of scarring. No more iodine was given. *C*, section from the same animal thirteen months after the section seen in *B* was taken and with the chronic infection still in place. Note the hyperplasia and the loss of colloid. The cells are columnar, and the picture resembles that sometimes seen in exophthalmic hyperplasia in the human being. Note the absence of scarring.

These animals, as we have reported elsewhere, had a high basal metabolic rate, increase in pulse rate and some of the other clinical signs seen in toxic goiter.

COMMENT

If the foregoing facts apply to human beings, we should expect to find nodular goiters more common in those regions in which the supply

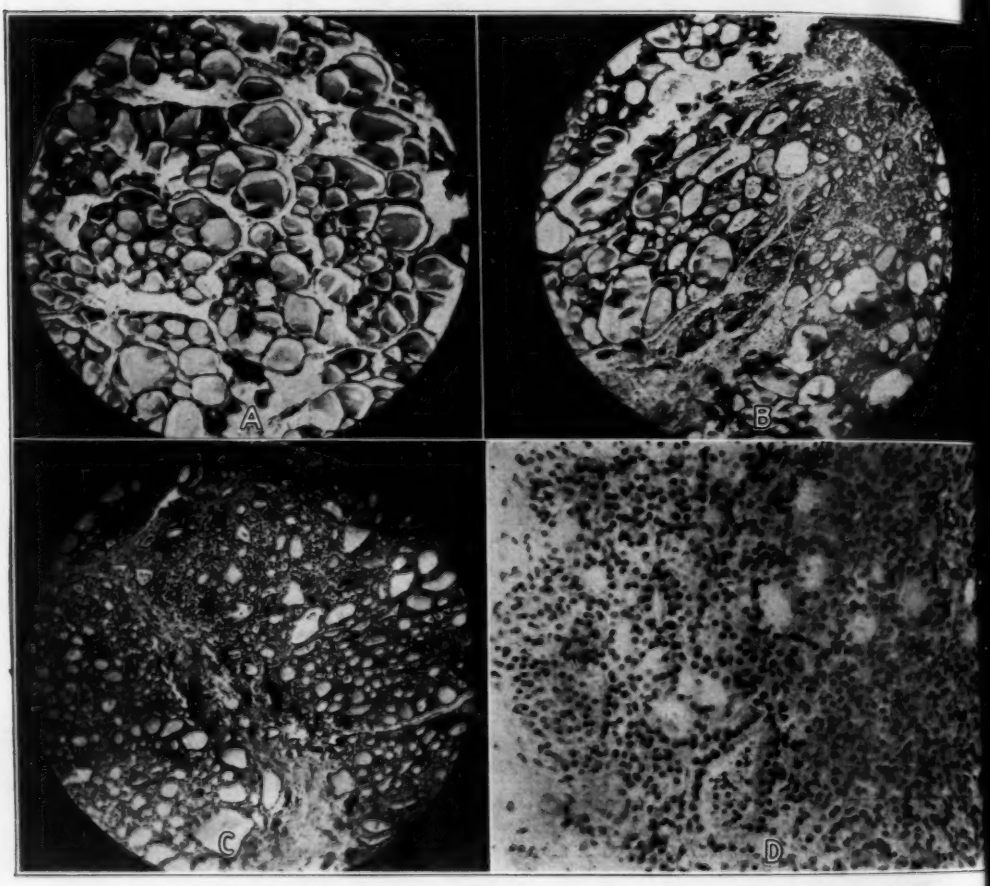

Fig. 7.—*A*, normal control section taken from the thyroid of an animal before the experiment was started. *B*, section from the same animal fourteen weeks later. Two weeks after a contaminated foreign body was buried in the muscles of the neck, compound solution of iodine was given for five days. This was discontinued and was fed to the animal again for two weeks before this section was made. Note the masses of fibrous tissue with acini showing both hypo-involution and hyperinvolution. The administration of iodine was stopped. *C*, section from the same dog eight months later. Note the dense bands of scar tissue surrounded by active thyroid tissue. *D*, higher power magnification of section *C*, showing the hyperplastic columnar cells and a picture resembling that in figure 6*C*. This is the effect of a long-standing focus of infection in this animal.

of iodine is scant. We should expect this because marked hyperplasia with involution would be more common. This is, of course, the case. Likewise, we should expect to find nodular goiters more common as the age of the individual increases. This, likewise, is true. In a series of 41 consecutive autopsies on human beings, most of them adults and none showing clinical goiters, we found that only 26.8 per cent could be classified as having normal glands, if our old criteria for a normal gland were used. A large portion of this 26.8 per cent showed some scar tissue and even small areas of focal hyperplasia. While we can not go so far as to state that the age of the patient can be reckoned by a study of the thyroid, as has been claimed by some, we feel certain that these changes are more common in older people. Wegelin [6] has demonstrated this conclusively in a long series of autopsies. He found, for instance, that at the age of 30 struma nodosa was present in 76 per cent of his 696 consecutive autopsies, struma diffusa in about 20 per cent and in about 10 per cent, the glands were found to be normal. This relationship was not constant, but varied with the age decades.

Until recently the opinion generally accepted in regard to the nature of the origin of the benign nodular goiters has been that they are true neoplasms, benign adenomas. This has been due not only to the striking morphologic similarity to adenomas elsewhere in the body but also to the difficulty in coordinating the clinical and pathologic pictures. Wölfler's [7] theory of the persistence of embryonal rests even in the adult gland has been a most popular one in spite of the fact that little substantial proof for it was ever offered. More detailed anatomic studies [8] have failed to demonstrate these interacinar fetal rests. It is, in fact, probable that the adult interacinar cells usually seen are tangential sections through other adult acini. Likewise, further clinical and pathologic studies [9] by several investigators have shown conclusively that it is possible for these so-called adenomas to develop during the course of involution of an actively hyperplastic gland.

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6. Wegelin, C.: Die Schilddrüse, in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926.

7. Wölfler, A.: Ueber die Entwicklung und den Bau des Kropfes, Arch. f. klin. Chir. **29**:1, 1883.

8. Rienhoff, W. F., Jr.: Gross and Microscopic Structure of the Thyroid Gland in Man, Arch. Surg. **19**:986 (Dec.) 1929. Williamson, G. S., and Pearse, I. H.: Anatomy of Special Thyroid Lymph System Showing Its Relation to the Thymus, Brit. J. Surg. **17**:529 (Jan.) 1930.

9. Rienhoff, W. F., Jr., and Lewis, D.: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79 (Jan.) 1928. Hertzler, A. E.: Pathogenesis of Goiter Considered as One Continuous Disease Process, Arch. Surg. **16**:61 (Jan.) 1928. Dunhill, T. P.: Toxic Goitre, Brit. J. Surg. **17**:424 (Jan.) 1928.

SUMMARY

We should like to emphasize the following points:

1. Increase in the functional activity of the thyroid gland is extremely common and is dependent on a number of factors. This increase in function is usually associated with definite morphologic changes that may occur to an extreme degree. If the stimulus is great enough, these changes may take place during the course of a few hours. A more or less mild stimulation of the thyroid gland over a relatively long period of time may produce hyperplastic changes similar to those seen in exophthalmic goiter.

2. Following involution brought about by the disappearance of the stimulus causing the increase in function or by artificial involution due to the administration of iodine, replacement of fibrous tissue occurs.

3. Repetition of this physiologic cycle may produce a nodular goiter similar to the so-called adenoma. The occurrence and location of these nodules is apparently dependent on the amount and the location of the fibrosis.

4. Experimental evidence is offered in support of these facts.

PLASMA CELL TUMORS OF THE NASAL AND NASOPHARYNGEAL MUCOSA *

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Most of the textbooks on pathology make little if any mention of plasma cell tumors except those occurring in the bone marrow, the plasma cell myelomas. Ewing,[1] however, in his work on neoplastic diseases, discussed extramedullary plasma cell tumors, and stated that in a rather numerous group of tumors of the mucous membranes and lymph nodes the growth is composed exclusively of plasma cells. He said:

> Considering their comparative frequency and rather peculiar clinical course, they have received inadequate attention. The growths occur chiefly in the nasopharynx, alveolar borders, tongue, lips, and cervical lymph nodes, but they have been observed in many other regions. The course is relatively slow, but they may recur after extirpation and become associated with a chronic cachexia. They are commonly classed as lymphosarcoma, but being, as a rule, benign processes with very indistinct neoplastic properties, it is highly important that they should be separated from the malignant lymphosarcoma. The structure presents a diffuse growth of more or less typical plasma cells.

Kaufmann [2] mentioned some cases of plasmacytoma which he said are counterparts of plasma cell aleukemic lymphadenosis. These special cases show granulation tissue, composed almost exclusively of plasma cells and lymphocytes, not only in numerous lymph nodes, but also in the liver and bone marrow. According to him, "A local plasma-cellular lymphogranulomatosa, so-called plasma-cellular granuloma or plasmacytoma, with a tumor-like appearance, adopts its favorite site in the nasal mucosa."

CASES FROM THE LITERATURE

In reviewing the literature, we have been able to find only twelve instances in which plasmacytomas of the nasal mucosa or nasopharynx have been described.

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* Submitted for publication, Dec. 10, 1930.

* From the Departments of Surgery and Pathology, Yale University, School of Medicine.

1. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 420.

2. Kaufmann, E.: Pathology, transl. by Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 1, p. 272.

In 1905, Schridde,[3] in a paper discussing granules in plasma cells, stated that he secured some of the material for the study from a tumorous involvement of the nose in a 40 year old man. The mass was found to consist of nests of plasma cells, between which capillaries were present. He gave no further details as to the clinical or pathologic observations.

Von Werdt,[4] in 1911, described the case of a 69 year old man, who had nasal speech and difficulty in swallowing, and who finally consulted a physician because of the former. A walnut-sized, freely movable tumor was found projecting from the posterior surface of the uvula. The outer surface was nodular and bluish red. There was no swelling of the glands of the neck. The mass was removed with a cautery snare. The wound healed quickly, and no recurrence of the process was evident at the time the case was reported. Pathologically, the tumor showed a transparent grayish-yellow outer portion and a central reddish-gray zone, the latter showing streaklike hemorrhages. The tumor was quite firm. Microscopically, it was seen to consist practically entirely of plasma cells, some of which showed mitoses, and other several nuclei. Cells with pyknotic nuclei and red bodies in the cytoplasm were found. (Hoffmann called these degeneration cells.) The capillaries were numerous; the stroma was scanty and contained pigment granules and hemorrhages.

In 1912, Vogt [5] wrote of a 20 year old man who had a rather sudden onset of pain in the neck and hoarseness. Examination revealed a tumor mass extending from the mastoid process to the jugular fossa, along the sternomastoid muscle. The structure was hard and freely movable. The posterior cervical nodes were not increased in size. The patient died in a "choking fit" four days after admission to the hospital. Autopsy showed that the posterior pharyngeal wall and the soft palate were almost double in thickness and seemed stiff and unyielding. The tonsils were swollen to walnut-sized masses which narrowed the pharyngeal passageway. On section, one could see that the thickening of the tissue was due to a pale gray infiltration of the submucosa by small nodules. Because of the great infiltration of the epiglottis, a stenosis of the laryngeal passage had been brought about. The thickening extended to the false vocal cords. The cervical lymph nodes on each side were the size of a walnut, not fused and easily removed. The cut surface was grayish and moist. In one node, pinhead-sized yellow masses were noticed. The axillary nodes were somewhat swollen, but those at the hilus were not enlarged. Microscopically, the uvula showed beneath the epithelium of its mucosa an infiltration of cells mostly of lymphocytic and plasma cell types. The latter frequently formed marked perivascular zones. The plasma cells were mostly of the usual type with an eccentric nucleus the chromatin of which presented a cartwheel-like arrangement. In many of the cells a perinuclear clear zone of cytoplasm was present. Sometimes cells with two nuclei located diametrically opposite in the cytoplasm were seen. More than two nuclei were only occasionally observed. Some cells had dark-staining nuclei. In a few areas the plasma cells were elongated and spindle-shaped, resembling fibroblasts. In the deeper portions of the mucosa, multinucleated giant cells of the Langhan's type were found in tissue infiltrated with lymphocytes and containing numerous vesicu-

3. Schridde, H.: Weitere Untersuchungen über die Körnelungen der Plasmazellen, Centralbl. f. allg. Path. u. path. Anat. **16**:433, 1905.

4. von Werdt, F.: Zur Kenntnis des Plasmocytoms, Frankfurt. Ztschr. f. Path. **6**:180, 1911.

5. Vogt, E.: Granulomatosis plasmacellularis colli, Frankfurt. Ztschr. f. Path. **10**:129, 1912.

lar nucleated epithelioid cells. No acid-fast bacilli were found. The posterior pharyngeal wall showed a picture similar to that in the uvula, except that no giant cells or epithelioid cells were present. The plasma cells extended along the blood vessels into the musculature, where they formed thick conglomerations of cells in the septums. The posterior part of the tongue, the epiglottis and the laryngeal wall showed marked infiltrations of plasma cells and also lymphocytes and a few polymorphonuclear leukocytes. The cervical lymph nodes were rich in plasma cells, especially near the fibrous capsule. A few of the nodes contained giant cells. The axillary nodes, inguinal nodes and the spleen likewise showed an increase of plasmacytes, but no Langhan's cells. Guinea-pigs given injections with the material showed no tuberculosis when killed later.

A fourth case was reported by Kusunoki and Frank[6] in 1913. This case was subsequently reported the same year in a different journal by Frank.[7] A man, aged 44, had noticed two years previously, at the angle of the left jaw, a pea-sized, hard mass. This became larger, and new masses appeared. The patient did not consult a physician until a year later, at which time respiratory difficulty was experienced. Roentgen therapy was given without results. About a year before admission the patient noticed tumors in his nasopharynx, and it became impossible for him to breathe through his nose. Epistaxis was a troublesome symptom. During two years he lost from 80 to 90 pounds (36.3 to 40.8 Kg.). The tumor of the left side of the neck was removed, and a month later that in the nasopharynx. The tissue from the latter consisted of ten pieces, the largest of which measured 3.5 by 3 by 1 cm. The remainder were about the size of an almond. The surfaces were irregularly nodular, firm but elastic, and varied from grayish white to grayish brown. The nodular masses were easily separated from the surrounding tissue. The cut surface was smooth, not protruding, and of the same color as the outer surface. On microscopic examination, a large number of typical plasma cells were found, especially grouped about blood vessels and capillaries (the latter being so rich as to give the structure a honey-combed appearance). Areas of necrosis were observed. The mucosa was preserved in scattered places while the submucosa showed a granulation tissue with some hemorrhage and some acellular hyaline connective tissue. The tissue from the neck consisted of twenty pieces which had not fused together, but were surrounded by loose connective tissue. The largest of these was 8 by 4.5 by 3.5 cm., the smallest about the size of a pea. The nodes were firm, nodular and grayish white. The cut surface was uneven and divided into many divisions by small and large white bands of connective tissue. In these places the larger masses were a dirty gray and showed rather poorly demarcated areas of necrosis. Microscopically, lymphoid structure was found preserved in only a few places. Plasma cells had almost completely replaced the lymphocytes. The remaining lymphoid tissue appeared atrophic with only a few follicles showing mitoses in the germinal centers. In some instances the differentiation between plasma cells and lymphocytes was not sharp. No transitional cells between these two types were found, however. Some plasma cells contained two, but rarely more, nuclei. In a few of

6. Kusunoki, M., and Frank, A.: Ueber ein plasmazelluräres Granulom, unter dem klinischen Bilde von Lymphomen der Halslymphdrüsen und geschwulstartigen Knoten in der Nasenschleimhaut, Virchows Arch. f. path. Anat. **212:** 391, 1913.

7. Frank, A.: Ueber ein Granuloma plasmacellulare. (Unter dem Bilde von Lymphomen in dem Halslymphdrüsen und geschwulstartigen Knoten in der Nasenrachenschleimhaut), Verhandl. d. deutsch. path. Gesellsch. **16:**115, 1913.

the plasmacytes were seen small, round, hyaline masses, the so-called "Russell bodies." Occasionally, these were present extracellularly. Mitotic figures were never encountered in the true plasma cells. The latter were grouped especially about blood vessels and were at times seen in the walls and even in the lumina. Capillaries were plentiful. Hemorrhages and areas of necrosis were observed. The patient died four years after the beginning of his illness, and showed at that time a swelling of the upper part of the thigh which was thought possibly to be also a plasmacytoma.

In 1913, Wachter [8] cited the case of a 48 year old woman who had suffered from bilateral deafness following attacks of cerebrospinal meningitis and otitis media. Twenty years before her admission, the present condition began with slight hoarseness noticed after prolonged talking, and with pain in the neck. On the present admission to the clinic, examination revealed a hard, slightly nodular tumor which arose from the floor of the right nasal cavity and from the inferior turbinate. It was clearly separated from the nasal septum. The middle turbinate showed a grayish-red unevenness. The tumor was reddish and bled slightly on motion. In the left nasal fossa, arising from its floor, was a small, hard swelling covered by normal mucosa. By means of posterior rhinoscopy, there was found on the posterior surface of the velum directly over the uvula a cherry-sized tumor, covered with normal mucosa, and situated on a narrow base. On the left false vocal cord, a red granulating growth with a broad base was found. The growths were excised but recurred locally about five and a half months later, with the addition of a new mass near the opening of the left eustachian tube. About ten months later, a mass the size of a cherry was found near the eustachian tube, and the growth in the right nasal fossa was seen to be increased in size. On the left, a thick fold of mucosal tissue was present. The velum and uvula were free. On microscopic examination, the tissues excised were seen to consist of large masses of plasma cells. These cells showed the usual eccentric nuclei with radially arranged masses of chromatin, and were quite uniform in size. Cells with two nuclei and a few with several, the so-called "plasma giant cells," were observed. Vacuolated cytoplasm was found in some. The plasmacytes were especially abundant about the walls of blood vessels where interstitial tissue was often lacking. The masses of plasma cells were divided into rectangular lobules by bands of connective tissue. In a portion consisting of a loose edematous reticular tissue, round cells, mast cells, dark-staining granules, as well as a few plasma cells, were seen.

The only instance of nasopharyngeal plasmacytoma we have found reported in English was that of Rogers [9] in 1920. He wrote of a 42 year old man, who about one year before had first noticed slight bleeding from the left nostril and the back of the nose. This continued for six months, when more severe hemorrhages from the nose and nasopharynx began. These hemorrhages commenced spontaneously, lasting from one to two days. About this time complete nasal obstruction occurred. At no time was there any pain. During the first year he sought advice from several physicians who prescribed nasal ointments or cauterized the nose. When seen by Rogers, he was anemic and the nasal obstruction was pronounced, but the septum was straight. The turbinates were pale and swollen, and a careful intranasal examination failed to reveal any bleeding points or

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8. Wachter, H.: Ein Fall von multiplem Plasmazytom der oberen Luftwege, Arch. f. Laryng. u. Rhin. **28**:69, 1913-1914.

9. Rogers, J. T.: Plasmoma of Nasopharynx, Canad. M. A. J. **10**:223 (March) 1920.

pathologic growth. Posterior rhinoscopy, however, demonstrated an uneven, granular-appearing, hemorrhagic mass completely filling the nasopharynx and seeming to arise from its vault. The surface of the tumor showed areas of fresh and old hemorrhage. On admission, the hemoglobin was found to be 40 per cent. General physical examination gave negative results. Both external carotids were ligated, stopping the hemorrhage. Six weeks later the growth was removed intact by means of a snare. Subsequent examination showed that the tumor took origin from the inferior border of the cushion of the eustachian tube and the adjacent surface of the soft palate. Microscopic preparations revealed that the growth consisted essentially of plasma-like cells, which were large and contained small, round, eccentric nuclei. There was little ground substance, and the surface was covered with transitional epithelium.

Facchini and Scalas,[10] in 1925, reported a plasma cell growth in a 47 year old woman. She had been married fifteen years and had never been pregnant. Her husband had acquired syphilis before marriage, but had had four years of intensive antisyphilitic treatment. At marriage his Wassermann test was negative, as it was at the time the case was reported. The patient for two years complained of difficulty in breathing through the right side of the nose. There had been no purulent secretion or other disturbance. On objective examination, it was noted that the right nasal cavity was completely occluded by a polypoid mass with a smooth, gray surface. The Wassermann and Meinicke tests were negative. The blood counts were normal. The tumor, which was attached to the upper and posterior part of the septum, was removed with little hemorrhage. The wound healed rapidly, and examination one year from the time of operation showed the nasal cavity to be free from any alteration except a slight cicatricial depression. The patient was given injections of mercuric chloride, following which the Wassermann reaction of the blood was again found to be negative. On gross examination, the tumor was found to measure 4 by 2 cm. The external surface was regular and smooth, and covered by a light red mucosa. The consistency was fibro-elastic. Around the base of the tumor were inserted small, round nodules of softer consistency and darker red color. On section, distinct zones could be observed with the naked eye or with only slight magnification. The peripheral part of the mass had a homogeneous aspect, gray and shining, that resembled the appearance of a common fibromyxomatous polyp. In the central regions were well circumscribed white islands of tissue, opaque and friable. The nodules in the vicinity of the pedicle also had these characteristics. The cut surface was gray and finely granular. Microscopically, a fine trabecular structure delineated areas of varying size containing the cellular elements. These were arranged some times in an alveolar manner and at other times in a cordlike fashion. The blood vessels were rather scanty with thin walls. The cells were oval or round, except where closely packed, when they were polygonal. The appearance of the nuclei and cytoplasm was typical of plasma cells except that perinuclear clear zones were not frequently observed. With the Unna-Pappenheim methyl-green pyronin stain, however, the characteristic reaction of the cells was seen. Giant cells containing two, three or more nuclei were occasionally encountered. A few large cells with less darkly staining nuclei and large nucleoli, others with pyknotic nuclei, and still others with vacuolated cytoplasm, were found. Mitotic typical and atypical figures were numerous.

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10. Facchini, G., and Scalas, A.: Su di un caso di fibro-mixo-plasmocitoma della cavita nasale, Arch. ital. di otol. **36**:331, 1925.

The observations made at autopsy on a 54 year old man who died several days following the partial extirpation of a tumor that filled the nasopharynx were described in 1926 by Rössle.[11] One tonsil and the nasal mucous membrane showed a widespread streptococcus lymphangitis. The tumor had grown through the clivus, filled the sphenoidal sinus, and reached past the roof of the pharynx to involve the upper part of the left nose. Two masses of tumor tissue were found on the posterior surface of the soft palate and two on the mucosa of the right antrum of Highmore. All the cervical lymph nodes and the sternum, ribs and skull showed neoplastic masses. Microscopically, all the growths were seen to be composed essentially of masses of plasma cells of different sizes, with a fine reticulum between the masses.

Hückel,[12] in 1927, discussed the case of a 46 year old workman who had had difficulty in breathing through his nose for six months, leading to an almost complete obstruction of the air passages. In his youth he had suffered from cervical adenitis. The general physical examination was without significant results. Rhinoscopic inspection showed a growth completely filling the whole nasopharynx with a small process the width of a finger extending down below the soft palate from a firm red mass. The right nasal cavity was narrowed by a deviation of the septum, while the posterior part of the left nasal cavity was obstructed by the growth. The mucosa of the pharynx and of the turbinates on both sides showed a slight catarrhal swelling. The maxillary sinuses were not involved. The growth was removed in several stages, partly through the nose and partly through the mouth. Bleeding was slight, and nasal respiration was restored. The origin of the growth was the mucosa of the posterior edge and of the wings of the vomer, and also of the nasopharynx. The thirteen pieces of tissue removed varied from the size of a pea to that of a bean. The external surfaces were partly dark brown and partly grayish white. They were unevenly nodular and fairly firm. The cut surfaces showed a similar appearance, were not very moist and were grayish white with here and there grayish-brown areas. On microscopic section, a rather uniform picture was seen, consisting of plasma cells packed closely together with a fine reticulum of connective tissue. In other places the stroma was denser and less cellular. In some areas the plasma cells formed columns between the dense strands. The plasmacytes contained often two, but seldom three nuclei. In rare instances mitotic figures were seen, but never amitotic division. A marked difference in the sizes of the plasma cells was not evident. Degenerative processes in the cells and "Russell bodies" were not found. The tissues were not especially vascular, and no particularly close relationship between the plasma cells and the vessels could be seen.

In the same year Pallestrini [13] described the interesting case of a man, 43 years of age, who for five months had had obstruction of the right nasal cavity and a purulent discharge. He also had had intermittent frontal headaches and pain occurring in the region of the distribution of the first and second division of the right trigeminal nerve. The remainder of his history was essentially unimportant.

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11. Rössle: Malignes Plasmozytom des Nasenrachenraumes, Schweiz. med. Wchnschr. **56**:302, 1926.

12. Hückel, R.: Ueber ein Plasmacytom des Nasenrachenraumes, Virchows Arch. f. path. Anat. **264**:172, 1927.

13. Pallestrini, E.: Su di un plasmoma atipico e maligno del naso, Arch. per le sc. med. **51**:175, 1927.

On physical examination, the positive signs were limited chiefly to the region of the head and neck. The right eye showed a mild exophthalmus. Vision and ocular movements were normal. There was a slight swelling in the right lower molar region. On examination of the nose, an enlargement of the inferior half of the right lateral wall was seen. The right cavity was completely occluded to the end of the vestibule by a pallid rose-colored neoplasm. The tumor was soft and showed some superficial ulcerated areas which were partially covered by pus. Some lymphadenopathy of the lateral cervical, supraclavicular, axillary and inguinal nodes was noted. The epitrochlear nodes were not enlarged. There were no clinical signs suggestive of syphilis. The Wassermann test was negative. At operation, the tumor was found to extend from the internal border of the right maxillary sinus to the region proximal to the inferior meatus, the inferior turbinate and the middle meatus. The maxillary sinus contained none of the neoplasm; however, pus was obtained from it as well as from the ethmoid cells. Grossly, the tumor consisted of a semi-oval, soft rose-gray mass the size of a walnut. Externally, it presented an irregular surface with many small round or oval ulcerations, which had irregular raised borders and were covered by a bloody and purulent exudate. The deeper portions were coppery red, and here and there many small soft areas were present. Microscopic preparations showed superficially a delicate connective tissue throughout which tumorous cells were seen. Those predominating were of the plasma-cellular type. Some of these were about the size of small lymphocytes; others were larger and round or oval. Some were irregular and had extensions of the protoplasm in fibrils which occasionally joined with similar processes from other cells. The nuclei of the first group were multilobulated. In some areas the cells were seen in chain formations separated in places by a delicate stroma directly surrounding the cells. Other areas showed epithelioid cells rich in protoplasm with single round nuclei, rich in chromatin. Throughout, some areas contained relatively few, small blood vessels, while in others a richness of blood vessels was noted. The patient returned to his home shortly after the operation. He was examined fifteen days later, and at this time a partial stenosis of the nasal cavity was found. He refused to submit to either a radical operative procedure or roentgen therapy. He died of cachexia and terminal meningitis six months later. Metastasis to the eyes had occurred.

Bronzini,[14] in 1928, described a case of a man 53 years of age who for four years had been suffering from nasal obstruction, mucopurulent nasal discharge and frequent sneezing. The positive physical signs were limited to the chest and nasopharynx. Examination of the chest revealed decreased phonation at the apex of the right lung and in the right interscapular region with also a slight increase of tactile fremitus in these areas. Roentgenograms demonstrated an opacity at the apex of the right lung and an engorgement of lymph nodes of the hilus of the right lung. On rhinoscopic examination, an irregular tumor mass was seen which arose from the region of the inferior turbinate and completely occluded the right nasal fossa. The tumor was soft and bled easily. Bleeding was not materially lessened by the application of epinephrine. The left inferior turbinate was moderately hypertrophied. The laboratory findings were within normal limits, and the Wassermann test was negative. At operation, the mass, together with the right inferior turbinate, was removed. The postoperative course was uneventful. On subsequent

14. Bronzini, A.: Di un voluminoso granuloma plasmacellulare del naso, Arch. ital. di otol. **39**:449, 1928.

examination eight months later, no recurrence of the growth was observed; the site of the scar, however, still appeared fresh as though the operation had been done only a few days previously. It presented a granular surface, which was hemorrhagic and necrotic in places. A foul-smelling, grayish discharge from the rhinopharynx was noted. The patient was asked to return for further treatment, but refused; he died a short time later of bronchopneumonia. Histologic examination of the tissue removed at operation showed it to consist externally of nasal mucosa. Beneath this there were trabeculae of connective tissue between which large masses of typical plasma cells were found. These masses were seen especially around blood vessels. Occasional cells with two nuclei were noted. No epithelioid or giant cells were present. Peripherally, some lymphocytic infiltration was observed. The microscopic preparations revealed no areas of degeneration or atypical proliferation.

Borri,[15] in 1928, presented two cases of plasma cell tumor. One was found in a 32 year old woman who had a history of syphilis, and occurred in the oropharynx. Because of its location and the fact that the diagnosis was not substantiated by microscopic studies, we are not including it in this series.

The second case was that of a man 56 years old who entered the hospital in December, 1923. At that time the right tonsil was found to be markedly hypertrophied, cryptic and pale. On the posterior pharyngeal wall was seen a neoplastic mass the size of a small almond, the structural characteristics of which were the same as those of the tonsil. Except for cervical lymphadenopathy, the remainder of the physical examination gave negative results. At operation the mass was removed and a tonsillectomy done. In 1926, the patient became aware of a sense of occlusion of the left nasal fossa. This early became complete. The patient was treated by a specialist who removed a large "meaty" mass. Following this the patient was well for two years, when the condition recurred. A similar operation was performed, which afforded relief for about a month and a half, at the end of which time the patient again began to have nasal occlusion and difficulty in deglutition. In November, 1928, he again entered the hospital for treatment with radium of a supposedly malignant tumor of the right tonsil. Examination of the oropharynx showed the right palatine tonsil to be markedly hypertrophied, cryptic, pale and divided into numerous lobes by fibrous septums. In places the mucosa showed definite ulceration. The tonsil had a hard, rubbery consistency to palpation. Rhinoscopy revealed in the left nostril a large, "meaty" pale mass with an irregular surface, which also showed some ulceration. Aside from the complaints described, the patient had always been in good health until the last year, when he became mentally senile. The Wassermann test was found to be positive. In the latter part of November the right tonsil was completely enucleated, and a biopsy was taken from the nasal tumor. Microscopically, the tonsil and nasal tumor mass showed much the same picture. The mucosa presented ulcerations in which small necrotic areas were seen. The deeper tissue showed a marked infiltration with an irregular round cellular element. In many of the cells the cytoplasm was granular, showing perinuclear semilunar lighter-staining areas. The nuclei were peripherally arranged, and the chromatin consisted of small triangular blocks, with their apexes pointing toward the center of the nucleus. In the center a small block was present, from which the other masses of chromatin radiated. In some areas, particularly surrounding blood vessels, numerous lymphocytic elements were

15. Borri, C.: Plasmomi delle fosse nasale e della faringe, Valsalva **5**:416, 1928.

present, some of which suggested plasma cells. The blood vessels, which were relatively infrequently seen, showed a proliferation of the intima and a poorly developed adventitia. While waiting for the tonsillar fossa to heal, the patient received insufflations of bismuth and arsphenamine powders. After ten days of treatment the nasal tumor was found to be reduced to one-third its original size. Later bismuth and iodine was given. On Dec. 30, 1928, on reexamination, the operative site was found to be healed, and the nasal growth to have disappeared.

AUTHORS' CASES

We wish to report two cases of plasma cell tumor of the nasal and nasopharyngeal mucosa which we have had the opportunity of studying.

CASE 1.—A Polish man, aged 34, came to Dr. Hammond's office with a complaint of "nose trouble" which had been present for years. Otherwise his history was essentially unimportant. Aside from the nasal condition, the general physical examination revealed nothing of note. A rhinoscopic study, however, demonstrated an irregular, gray tumor mass which filled the entire interturbinate space in the right nasal fossa. This appeared to arise from the turbinate bones. The tumor was partially covered by a yellowish-gray exudate. The entire tumor was removed at operation, and the wound healed nicely. Subsequent examinations, the last a year and a half after operation, did not reveal any evidence of recurrence.

Pathologic Study.—Gross: The specimen consisted of four irregular pieces of tissue which averaged about 2 cm. in diameter. They had been preserved in alcohol and were opaque and yellowish gray. On section, the cut surfaces presented an uniform, soft gray appearance.

Microscopic: The material was fixed in alcohol and a solution containing 1 part of "solution of formaldehyde U. S. P." and 9 parts of water. A portion was embedded in celloidin and another in paraffin. The preparations were stained with hematoxylin-eosin. No Unna-Pappenheim methyl-green pyronin or other special stains were made. In some of the microscopic preparations the external surface of the tissue was seen to be partially covered by a thin layer of stratified squamous epithelium. Beneath this, numerous moderately thick trabeculae of fibrous tissue, containing oval or spindle shape cells, divided the tissue into rather small irregular areas which were loosely filled with cells. The latter consisted chiefly of rather small round or oval cells with homogeneous grayish-blue cytoplasm containing spherical nuclei, many of which were eccentrically located. The chromatin of these nuclei had a radial arrangement which gave the so-called cartwheel appearance. These appeared to be typical plasma cells and were for the most part fairly uniform in size and shape. Here and there, however, larger cells which were about twice the size of the surrounding cells, but which were otherwise identical in structure, were seen. An occasional larger cell containing two nuclei was found and rarely those containing three nuclei were present. Scattered throughout the large groups of cells fairly numerous lymphocytes and polymorphonuclear cells were seen. There were also found irregularly throughout, fairly numerous, rather large, round or oval cells which had sharp margins and poorly staining vacuolated cytoplasm. These contained small, oval, somewhat vesicular nuclei. This type of cell was extremely difficult to classify. In no place did the plasma cells appear to invade the septums of fibrous tissue. Anaplasia was not distinct; no mitotic figures in the plasma cells were seen and no areas of hemorrhage or frank necrosis were found. In several areas capillaries were rather numerous.

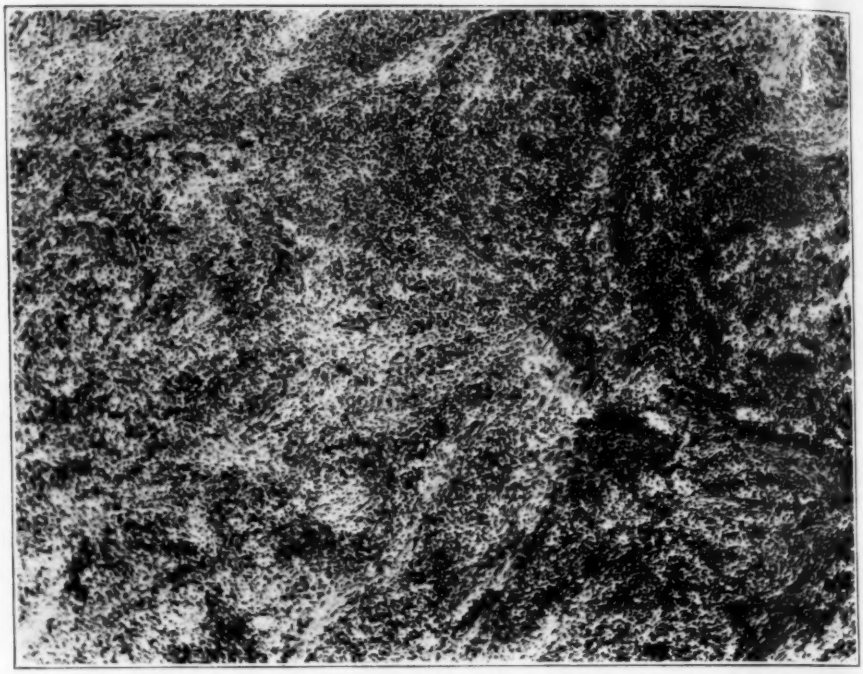

Fig. 1 (case 1).—Photomicrograph showing dense distribution of plasma cells. The stroma is fairly dense. Hematoxylin-eosin stain; × 75.

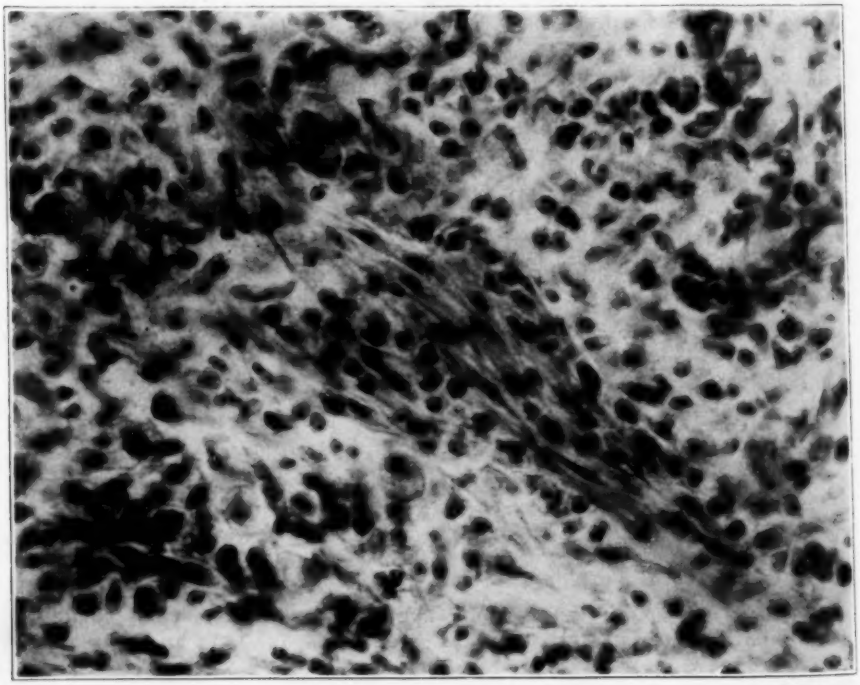

Fig. 2 (case 1).—Photomicrograph showing in more detail the plasma cells and the rather marked fibrous stroma. Hematoxylin-eosin; × 300.

CASE 2.—A man, aged 60, a native of Sweden, on admission to the New Haven Hospital, May 5, 1930, gave the following history: For the past two years the right side of his nose had been obstructed, and he had noticed a moderate postnasal discharge. He had used nasal drops for some time with no improvement of symptoms. In September, 1929, a small "growth" was removed from the right nasal fossa. The clinical diagnosis at that time was nasal fibroma. No pathologic examination of the tissue was made. Following the operation the patient had some relief from symptoms, which, however, lasted only a short time. The symptoms again became marked, and on examination it was found that the tumor had recurred. The patient had no headaches or dizziness. He gave a history of having had severe attacks of tonsillitis occurring almost every winter for several years. About two weeks before admission, a small tumor was removed from under his left arm. No pathologic examination of the tissue was made. The remainder of his history was irrelevant.

On physical examination the patient was seen to be moderately well developed and well nourished. Except for the nasal condition, the physical examination gave essentially negative results. On inspection of the nose, the septum was seen to be somewhat deviated to the left and in contact with the left middle turbinate. Both inferior turbinates were enlarged. The right middle turbinate was moderately hypertrophied. In the right nasal cavity a raised, somewhat lobulated tumor mass, about 3 cm. in length and 1.5 cm. in width, was seen extending from the middle meatus over the middle turbinate. It was partially covered by a yellowish exudate. A similar but somewhat smaller tumor mass was seen extending downward from the fossa of Rosenmüller on the right. The Wassermann test and urinalysis gave negative results. The blood count showed: red blood cells, 5,400,000; hemoglobin, 110 per cent (Sahli); white blood cells, 8,000, with a differential count of 59 per cent polymorphonuclear leukocytes, 34 per cent lymphocytes and 7 per cent large mononuclear cells. Roentgenograms of the nasal sinuses were negative, and no pathologic process of the bone was demonstrated in the skull. The clinical impression was fibroma of nasopharynx. On May 6, 1930, under local anesthesia, incisions were made on either side of the tumors with alligator scissors, and they were then removed by means of a snare. Only moderate bleeding was encountered. Three days later the sites of the tumors were irradiated, 33.75 millicurie hours of irradiation being used. Following this, the patient was discharged. Subsequent examinations showed the operative sites to be healed. To date there is no evidence of recurrence (12-1-30).

Pathologic Study.—Gross: The gross specimen consisted of several pieces of tissue, the largest of which measured about 4 by 2 by 1 cm. Externally, the tissue was grayish white and smooth. To palpation, the tumor felt moderately soft. On section, the tissue cut easily, the cut surfaces presenting a gray fibrous appearance, throughout which numerous rather large dark bluish-red hemorrhagic areas were seen.

Microscopic: The material was fixed in neutral formaldehyde, 10 per cent, and preparations stained with hematoxylin-eosin and methyl-green pyronin. Others were stained according to Mallory's and to van Gieson's technic for connective tissue, and by Haythorne's and Kinyoun's methods for spirochetes and acid-fast bacilli, respectively. Several of the microscopic preparations showed the nasal mucosa, consisting of an epithelial portion with a surface layer of columnar epithelium, occasionally showing cilia, and one or two rows of more basally located cuboidal cells. Below this there was a layer of rather loosely arranged

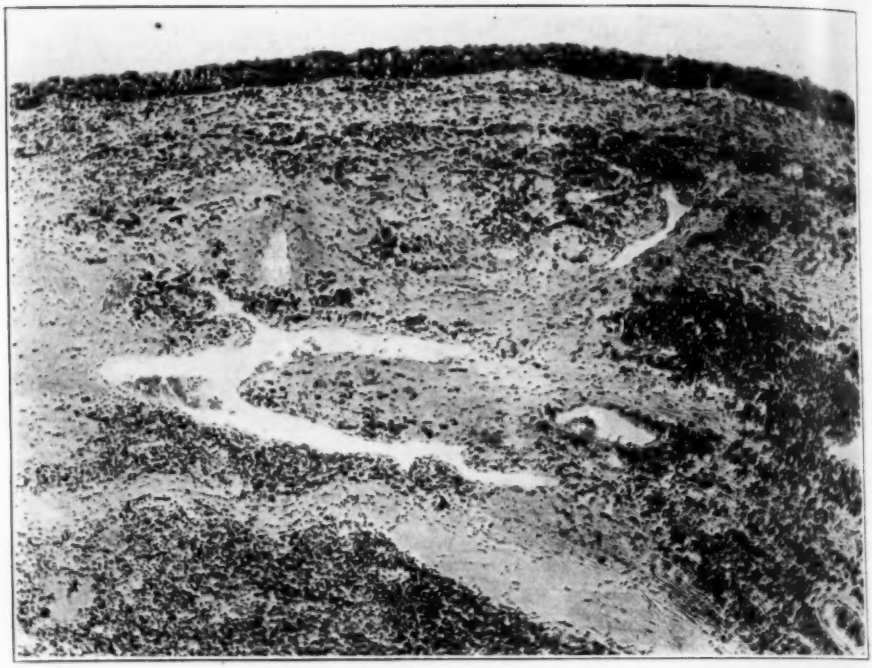

Fig. 3 (case 2).—Photomicrograph showing the plasma cell infiltration of the mucosa. Hematoxylin and eosin stain; × 70.

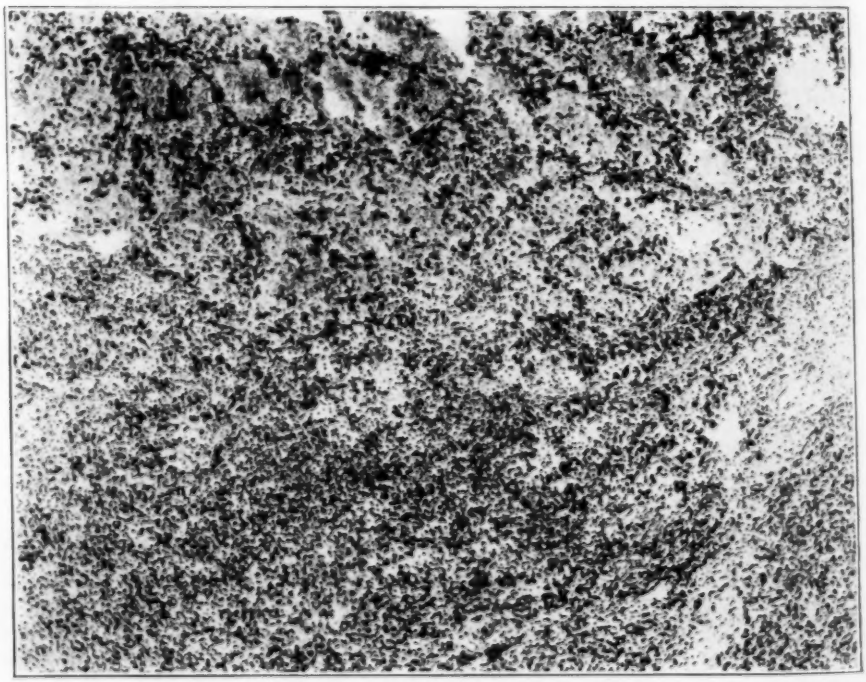

Fig. 4 (case 2).—Photomicrograph showing the density of the plasma cell accumulation with areas of hemorrhage in the upper portion of the plate. Hematoxylin-eosin stain; × 85.

fibrous tissue in which numerous capillaries and blood spaces were seen. In this tissue, especially just beneath the surface epithelium, were a few scattered polymorphonuclear neutrophilic leukocytes. Scattered small round cells of the lymphocytic type were present and likewise plasma cells with abundant pink or gray homogeneous cytoplasm and rather dark, usually eccentrically placed nuclei. The latter, as a rule, showed a more densely arranged chromatin with less of the radial distribution than is usually found in these cells. Deeper in, the tissue consisted of large irregular masses of apparent plasma cells. These groups of cells were not sharply demarcated from the overlying mucosa, and in places extended irregularly in finger-like processes into that layer. The individual cells varied considerably in size and shape, some being only about two or three times the size of a lymphocyte, while others were many times that size. Where the cells lay free, they tended to be round or oval, but where they were found close together their outlines were frequently irregular. The cytoplasm had a grayish blue tint with hematoxylin-eosin stains. The nuclei were spherical, and in many cases eccentric in location. The chromatin in most nuclei formed little knotlike masses, the radial arrangement of which gave the nuclei the typical so-called cartwheel appearance. About a large number of the nuclei, the cytoplasm showed a clear semilunar zone, which has been frequently described as being present in plasma cells. Cells with two or even three nuclei, and rarely more, were seen, these cells usually being larger than the general average, but occasionally no greater in size. Throughout the sections were found scattered cells which corresponded in size and shape with the other plasma cells of the tumor, but which had pinkish-red, denser cytoplasm and usually darker, less typical nuclei. Where the plasmacytes were densely packed, the cell outlines were often indefinite, but a true sheetlike arrangement of the cells as often seen in carcinoma was not observed. The methyl green pyronin preparations did not show the nuclei of the cells to be stained green and the cytoplasm red, as is typical of plasmacytes, but this was probably due to the fact that the tissue was fixed in formaldehyde rather than alcohol. However, the general appearance of the cells, with their homogeneous cytoplasm, perinuclear clear zones and the radially arranged chromatin of the nuclei was typical of plasma cells, and leaves little doubt that they were of this nature. Moreover, the similarity of the cells in our cases to those described by other authors who successfully employed the Unna-Pappenheim stain, is extremely close. The stroma, as a rule, was slight, with only a few delicate strands separating the individual cells of the masses in most places. In other areas, fewer plasma cells were seen, and here the stroma was looser and showed spindle shape or oval connective tissue cells, small capillaries, and likewise numerous extravasations of red blood cells. No frank areas of necrosis were found. Lymphocytes were scattered among the plasma cells, but in a few places formed the predominant element. Mitotic figures in the plasmacytes were but rarely seen. Occasionally there were encountered large cells with several rather dark-staining nuclei, often irregular or bean-shaped. These cells did not in their appearance suggest plasma cells. Careful search was made for both spirochetes and acid-fast organisms in the sections prepared with the appropriate stains, but none was found.

Dr. Samuel Hammond of Hartford, gave us the clinical history of the first case and Dr. Wilmer Allen, pathologist of the Hartford Hospital, the pathologic material. Dr. Charles T. Flynn, assistant clinical professor of otolaryngology, Yale University School of Medicine, gave us permission to report the second case.

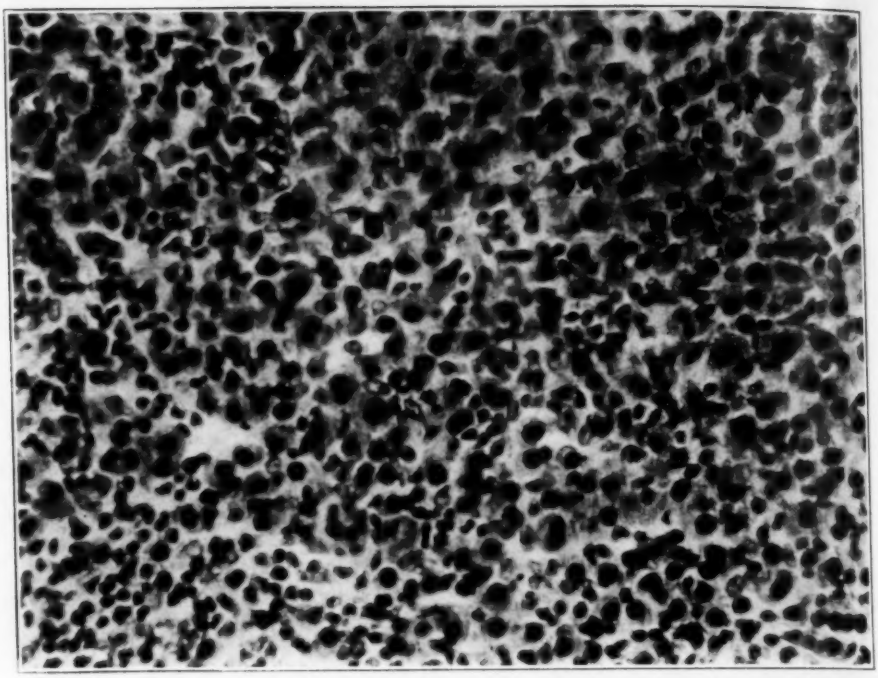

Fig. 5 (case 2).—Photomicrograph demonstrating the type of plasma cells. The nuclei appear more darkly stained than they actually were. Hematoxylin-eosin; × 300.

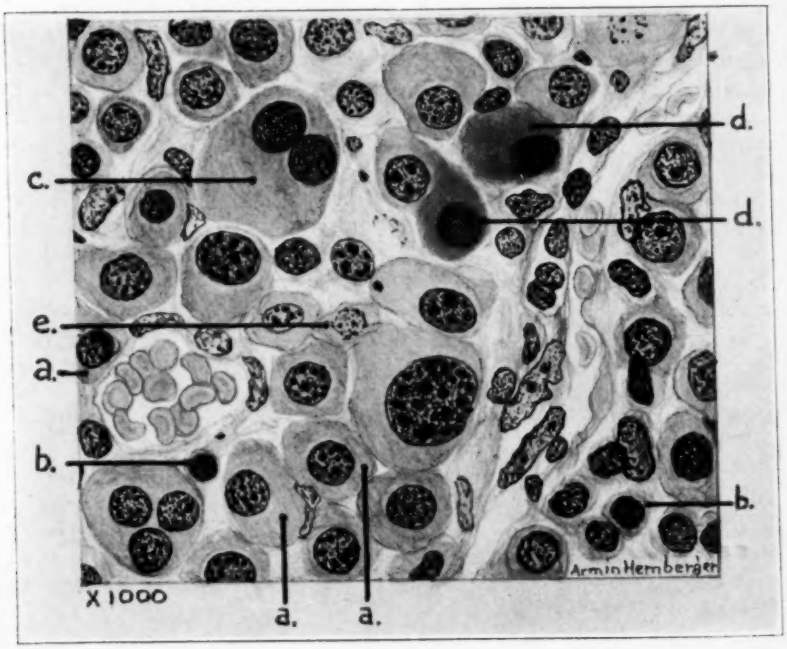

Fig. 6 (case 2).—Drawing showing the cellular detail: *a*, typical plasma cells; *b*, lymphocytes; *c*, multinucleated plasma cells; *d*, plasma cells with pyknotic nuclei and dark red staining cytoplasm; *e*, plasma cell with poorly defined nuclear membrane. Hematoxylin-eosin stain; × 1,000.

Summary of Cases

Author	Date	Age	Sex	Symptoms, Duration, etc.	Location
Schridde[3].....	1905	40	M	Not given	Nose
von Werdt[4]...	1911	69	M	Difficulty in swallowing and nasal speech; growth excised, and wound healed quickly with no recurrence	Posterior surface of uvula
Vogt[5].....	1912	20	M	Sudden onset of hoarseness, pain in neck; patient died before operation; necropsy done	Uvula, pharynx, tonsils, epiglottis, larynx, cervical, axillary and inguinal lymph nodes
Kusunoki and Frank[6] Frank[7]	1913	44	M	Lump size of pea at angle of left jaw; two years later tumor in nasopharynx with respiratory difficulty; epistaxis, loss of weight; died four years after onset, showing swelling of upper part of thigh	Nasopharynx, left side of neck
Wachter[8].....	1913	48	F	Onset twenty years previous with slight hoarseness and pain in neck; operation; recurred locally; again removed; recurrence	Floor of right nasal fossa and inferior turbinate; floor of left nasal fossa; velum above uvula; left false vocal cord
Rogers[9].....	1920	42	M	Severe attacks of epistaxis for period of a year, nasal obstruction; growth removed; uneventful recovery	Inferior border of cushion of eustachian tube, and adjacent surface of soft palate
Facchini and Scalas[10]	1925	47	F	For two years nasal obstruction; operation; no recurrence after a year	Right nasal cavity from posterior portion of septum
Rössle[11].....	1926	54	M	Nasal obstruction; extirpation of tumor filling nasopharynx; death several days later; necropsy	Tumor grown through clivus, filled sphenoidal sinus; roof of pharynx involving upper part of left nose; posterior surface of soft palate; mucosa of left antrum of Highmore; cervical nodes, sternum, ribs, skull
Hückel[12].....	1927	46	M	Difficulty in nose breathing for six months with almost complete nasal obstruction	Nasopharynx and mucosa of posterior edge of wing of the vomer
Pallestrini[13]..	1927	43	M	Nasal obstruction; nasal discharge; frontal headaches; pain in region of the distribution of first and second divisions of the fifth nerve, right	The inferior half of the right lateral wall of nose
Bronzini[14]....	1928	53	M	Nasal obstruction with mucopurulent discharge; frequent sneezing	Inferior turbinate, right
Borri[15].....	1928	56	M	Difficulty in eating solid food; nasal occlusion; operation; recurred locally; operation; recurrence; disappearance following antisyphilitic treatment; Wassermann test positive	Left nasal fossa; right palatine tonsil; posterior pharyngeal wall
Authors' case 1	1930	34	M	Nasal obstruction; tumor removed; no recurrence	Right nasal fossa filling the entire interturbinate space
Authors' case 2	1930	60	M	Obstruction to right nose of two years' duration; nasal discharge; small growth removed; considerable improvement for a short time; recurrence of tumor; tumor again removed; no recurrence to date	Right nasal fossa extending from the middle meatus over the middle turbinate; fossa of Rosenmüller

COMMENT

While the series of cases that we have collected is too small to justify any general conclusions as to the age and sex incidence in cases of the tumors described, it is interesting to note that of the fourteen cases, twelve occurred in males and only two in females. The youngest patient was 20 years of age, while the oldest was 69. Of the fourteen patients, twelve were 40 years or more of age. The predominant symptoms that caused the patients to seek medical care were nasal obstruction (eleven cases); difficulty in deglutination (two cases); epistaxis (two cases), and hoarseness (two cases). In the instances in which hoarseness was a chief complaint the patients were found to have tumors in the pharynx as well as in the nasal or nasopharyngeal regions. Several patients complained of more than one of the foregoing symptoms. In summarizing the cases according to anatomic location, we found that five occurred in the nose alone; one in the nasopharynx; while in two instances both these sites were involved. In some instances tumors were also present in the oropharynx, larynx, lymph nodes or other sites.

Morphologically, the tumor masses were characterized grossly in the majority of the cases by a coarsely nodular or more finely granular appearance. They varied in size from those which almost or entirely filled the nasal or nasopharyngeal cavities to smaller masses from 1 to 3 cm. in diameter. Some had flat bases, while others were definitely pedunculated. The majority of the masses were firm. In our second case, however, the tumors were soft. The color was pale or pale gray, bluish red or dark brown, apparently resulting from congestion and hemorrhage. The latter was noted definitely on gross examination in three or four instances. Microscopically, all of the tumors were marked by the abundance of undoubted plasma cells. In only one or two instances were these described as being uniform in size and shape. More frequently they showed a good deal of variation in those respects, and cells containing two nuclei were commonly noted. Plasmacytes with more than two nuclei, the so-called plasma giant cells, were not infrequently observed. The nuclei were usually round or oval with radially arranged masses of chromatin. Multinucleated giant cells of the Langhan's type were seen by only one observer (Vogt [5]). Degenerated cells were described by only one or two authors. An obvious necrosis involving the plasma cells and interstitial tissue was not a frequent observation, but was mentioned by Frank.[7] Hemorrhage was observed microscopically in those tumors in which it was manifest grossly. A particular abundance of capillaries was noted by some, and others found that the plasma cell groups were especially numerous in the vicinity of the blood vessels, often forming perivascular collars.

An almost universal observation was the delicacy of the interstitial connective tissue which formed a fine reticulum in which the plasma cells rested in rather closely packed masses. Denser trabeculae were observed in only a relatively few instances. Lymphocytes were quite numerous according to some descriptions, at times dominating the picture in small areas. Other observations of less frequency were the presence of rare mitotic figures and of eosinophils (one case). Polymorphonuclear neutrophilic leukocytes observed in both of our cases were in the second restricted to the mucosa covering the tumor, and formed no part of the masses rich in plasma cells.

In regard to these plasma cell tumors, the much debated question arises as to whether they are true neoplasms, or whether they have an inflammatory origin. Moreover, if the former is true, should they be considered as benign or malignant; and if the latter, is there a specific infectious agent, or is the inflammatory etiology unknown? In this discussion we will not enter the controversy as to the origin of plasma cells. It may be stated, however, that there are two main theories. One is that the plasma cells are derived from lymphocytes, the other that they come from the fixed tissue (the fibroblasts of the adventitia of the blood vessels). The first view is the one most commonly held.

Wachter [8] considered that his case was to be classified from the clinical picture in the group of localized benign tumors, although the same plasma cell forms were seen as those described in the cases which were considered by other authors to be malignant. He believed that there was no pathologic evidence for considering it as having a chronic inflammatory basis. The same attitude was manifested by Facchini and Scalas [10] in their discussion of the growth which they described. That such a structure could be a fibromyxoma with an infiltration of plasma cells was admitted, but they were of the opinion that their case lacked the evidences of chronic inflammation and of a granulomatous nature, the chief rôle being played by the cellular elements. The explanation of the etiology on a syphilitic basis was ruled out, they believed, by the repeatedly negative Wassermann tests and lack of specific clinical history and physical signs. Moreover, the epithelioid cells, lymphocytes, fibroblasts, foci of caseous necrosis and of sclerosis usually found in syphilitic processes were wanting, as well as a lack of evidence of endarteritis obliterans and other vascular changes. That a neoplasm of plasma cells could take origin from the nasal mucosa was thought by them to be explainable, as it had been demonstrated by others that numerous plasma cells exist in the normal mucosa. What factors might cause these plasma cells to multiply in such a manner as to form a neoplasm, they realized was difficult to determine.

and a discussion regarding their nature would lead one into the difficult field of the general etiology of tumors. They called especial attention to the fact that a year following the removal of the tumor there was no evidence of recurrence, and they therefore considered that their case was an example of a benign plasmacytoma, as opposed to most of the other cases described, which originated in the bone marrow or lymphatic glands and gave rise to metastases to other parts of the skeleton or even to the mucosa. Facchini and Scalas concluded that plasmacytomas of the nasal mucosa are often of benign nature. Hückel [12] felt likewise that in his case the description justified the classification of the plasma cell tumor as a new growth as opposed to a simple reactive cellular infiltration.

Among those cases which were definitely considered to be of a malignant nature, that of Rössle [9] is outstanding. He concluded that the tumor which he described was unquestionably malignant on the basis of its invasive character. Rössle questioned whether in such tumors metastases to mucous membranes could occur through implantation. In this instance it was doubtful as to whether the point of origin was the mucosa or the bony posterior wall of the nose. He suggested that a malignant plasmacytoma is not so rare as generally believed, and perhaps in some instances has been unrecognized. Von Werdt [4] believed that the plasma cell tumor described by him could be called a new growth because of its circumscribed form, the type and number of the cells, and the relation to blood vessels, and stated that it belonged to the group of sarcomas. He called it a plasmacytoma. Pallestrini [13] believed that his case, which was unquestionably malignant (as shown by its course), should not be called a plasmasarcoma. He preferred to classify it as an atypical and malignant plasmoma to stress better the derivation and structure of the neoplasm. Vogt [5] considered that his case was a neoplasm which had metastasized to the lymph nodes. In his conclusions, however, he termed it a plasma cell granuloma and suggested that possibly the etiologic agent was an "unknown noxious one."

An inflammatory origin for the masses of plasma cells was advanced by Borri.[15] He believed that one must admit that with a general infection of long duration, such as tuberculosis or syphilis, there is a tendency toward a defense reaction characterized by the production of plasmacytes. He considered both of his cases to have a syphilitic basis. In these tumors the character and type of the cellular elements were, in his opinion, not indicative of a true neoplasm. He gave these tumors the name of "granuloma plasmacellulare" as did Vogt, who perhaps employed that term inadvisedly since he had previously called the condition a neoplasm with metastases.

Still other writers, after discussing various possible ways of grouping the tumors, reach no definite conclusions. Schridde [3] stated that his case could not be considered a myeloma (malignant plasmoma) since tests for albumose in the urine were negative, and other evidence for this diagnosis was lacking. He expressed no definite views as to its nature. Kusunoki and Frank [6] gave their tumor the name of plasma cell granuloma, which they believed was due to an unknown toxic agent acting on the vessel walls causing a transmutation of the fibroblasts of the adventitia to plasma cells. Frank,[7] in a subsequent article discussing the same case, outlined arguments for and against the diagnosis of the tumor as a true neoplasm, a "leukemic-pseudoleukemic" mass, or a granuloma. The history and clinical course did not support the diagnosis of a true neoplasm. Also the absence of invasion, and the formation of plasmacytes from the adventitial cells, rather than from preexisting plasma cells, were, in his opinion, against that hypothesis. If one defines the "leukemic-pseudoleukemic" tumor formation as an hyperplastic disease of the hematopoietic system, he felt that his case could not be so considered since the plasma cells there were not derived from specific elements of the blood-forming organs. Arguments for the granulomatous nature, aside from the localization, were the similarity of the process in the cervical nodes and nasopharyngeal mucosa, the marked growth of the adventitial cells of the vessels with transition into plasma cells, the latter cells themselves, the richness of the capillary formation and the presence of necrosis and hemorrhage. In regard to the etiology in his case, he stated that no micro-organisms were found. Neither was there support from the clinical data nor the histologic signs for the diagnosis of tuberculosis or syphilis. In the case described by Bronzini,[14] that author considered that he was dealing with a neoplasm which was either a plasmacytoma or granuloma plasmacellulare. He excluded plasmasarcoma because of the clinical course. Syphilis was excluded by the history, physical examination and negative Wassermann test. He believed that sufficient criteria for the diagnosis of the growth as a true neoplasm were not present and he therefore preferred to call it a granuloma.

Fairly numerous descriptions of plasma cell tumors that were located extramedullarly in other portions of the body than the nasal or nasopharyngeal mucosa have been made. Some of these masses were accompanied by similar involvement of bony structures, but others did not have this complication. We will outline here the views of several of the authors concerning these tumors, since many of them are similar to ours structurally and vary only in their different locations and perhaps clinical course. Among those who claimed a benign neoplastic nature

for the plasma cell masses was Boit,[16] who wrote in 1907. He described an involvement of the false vocal cord by tumorous plasma cells, and stated that on histologic grounds the prognosis was unfavorable, since both of the plasma cell tumors which had been previously reported were of malignant nature. The lack of recurrence shown on examination several months following operation, however, suggested to him that possibly the plasma cell tumor was not malignant and perhaps bore the same relation to a malignant plasmacytoma that a lymphoma does to a lymphosarcoma. Hedinger,[17] in 1911, described a plasmacytoma of the scalp which was combined with a malignant adenoma of the sweat gland. He felt that a long-standing inflammatory process caused the plasma cells to proliferate after the nature of tumor cells, until a definite large granulation plasmacytoma resulted. Kaufmann,[2] in discussing this case, stated that there are transitions from simple reactive infiltration to plasma cell granuloma, distinguished by marked cellular proliferation. Deutschmann[18] claimed, however, that these growths are tumors only by exclusion, since the etiology of an inflammation cannot be determined.

A malignant nature was manifested in the case described by Hoffmann[19] in 1904, in which masses of plasma cells were found in the skull, sternum, clavicle, vertebrae, rib and liver. Micheli,[20] also in 1904, reported a similar case in which, in addition to bone marrow masses, infiltration of the plasma cells was present in the liver and spleen. He considered this a plasma-cellular pseudoleukemia. In neither of these was there any involvement of the surfaces of the skin or of the mucous membranes. We are of the opinion that these were probably true multiple myelomas. Sternberg and Menne, cited by Kaufmann,[21] believed that the case of Hoffmann should be separated from the true myelomas because of the metastases to the liver. However, actual metastases to internal organs in multiple myeloma are not uncommon. A careful review of cases made by Geschickter and

16. Boit, H.: Ein Fall von Plasmocytom des Sinus morgagni, Frankfurt. Ztschr. f. Path. **1**:172, 1907.

17. Hedinger, E.: Zur Frage des Plasmacytoms, Frankfurt. Ztschr. f. Path. **7**:343, 1911.

18. Deutschmann, F.: Das Plasmom, die hyaline und amyloide Degeneration der Konjunktiva, Ztschr. f. Augenh. **27**:242, 1912.

19. Hoffmann, R.: Ueber das Myelom, mit besonderer Berücksichtigung des malignen Plasmoms, Beitr. z. path. Anat. u. z. allg. Path. **35**:317, 1904.

20. Micheli, F.: Pseudoleucemia plasmacellulare, abstr., Folia haemat. **1**:440, 1904.

21. Sternberg and Menne, cited by Kaufmann, E.: Pathology, transl. by Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 2, pp. 1216-1222.

Copeland [22] revealed rather numerous instances in which visceral metastases were reported. A case described by Maresch [23] showed plasma cell involvement of bone marrow, lymph nodes, spleen and liver. Here the tumors of the bone marrow were not prominent. He called this a plasma-cellular granuloma. It might well be considered, however, along with those of Hoffmann and Micheli as a multiple myeloma. Kaufmann [21] recognized the occasional occurrence of nodular myeloma in various viscera which produce the picture of metastatic nodules, but he believed that typical myelomas are not malignant tumors and that these heterotopic masses are not true metastases such as occur in malignant neoplasms, but are merely an expression of a systemic disease of the hematopoietic apparatus. In this connection we might mention the case of Ghon and Roman [24] in which a diffuse plasma-cellular hyperplasia of the lymphatic hematopoietic system was found, analogous to changes seen in leukemia and pseudoleukemia. Practically all of the organs as well as the bone marrow showed a varying degree of infiltration of the plasma cells. In discussing a plasma cell tumor of the pleura, Klose [25] held that it was malignant, since it invaded the adjacent soft parts.

An inflammatory nature was suggested for a number of localized plasma cell tumors occurring in various sites such as the conjunctiva (Pascheff, Rados, Porkowsky, Franke and Baurmann); the lip (Kaufmann); anus (Albrecht) and jaw (Pirone). These authors were cited by Hückel.[12] Baurmann considered carefully the conflicting question of the etiology and nature of the tumors. He maintained that the criteria advanced by Boit and von Werdt to support their diagnosis of plasmacytomas as benign tumors were not in any sense conclusive. He also rejected Deutschmann's claim that the diagnosis of tumor was made only by exclusion, and held that it is justifiable to consider accumulations of plasma cells as an anatomic evidence of inflammation. Alagna,[26] who made a rather extensive study of nasal polyps, divided them into two groups, which he called the serous and granulomatous. Definite structural differences were noted. In the serous type, a watery stroma, often cystic, was present, with only scattered cellular elements

22. Geschickter, C., and Copeland, M.: Multiple Myeloma, Arch. Surg. **16:** 807 (April) 1928.

23. Maresch, R.: Ueber ein plasmazelluläres Lymphogranulom, Verhandl. d. deutsch. path. Gesellsch. **13:**257, 1909.

24. Ghon, A., and Roman, B.: Ueber pseudoleukämische und leukämische Plasmazellen-Hyperplasie, Folia haemat. **15:**72, 1913.

25. Klose, H.: Ueber das Plasmocytom der Pleura, Beitr. z. klin. Chir. **74:**20, 1911.

26. Alagna, G.: Die Plasmazellen bei Ohren-Nasen und Kehlkopfkrankheiten, Virchows Arch. f. path. Anat. **204:**136, 1911.

such as lymphocytes, neutrophilic polymorphonuclear cells and plasmacytes. In the granulomatous form, the polyps consisted of a structure identical with granulation tissue. In these the plasma cells were the predominant element, and in places they were so closely packed that it was difficult to find other types of cells. He believed that this type occurred only associated with infections of the nasal sinuses. He further suggested that the formation of true plasmomas from the granulomatous polyps may result from the continuous irritation of the secretions from the diseased sinuses. An association with syphilis was pointed out by Bunger (quoted by Hückel [12]), who mentioned a case of primary syphilitic infection (spirochetes demonstrated) in which a diagnosis based on the microscopic signs of plasmacytoma was previously made by a competent observer. More recently, di Vestea [27] described a massive plasma cell involvement of both tonsils in an 82 year old man. The patient's Wassermann reaction was strongly positive, and the lesions disappeared following treatment with sodium caccodylate and mercury. He stated that in the simple hypertrophic form of syphilitic tonsillitis, a transition may take place to a plasmomatous hypertrophic form which represents a true neoplastic tissue of a specific inflammatory type. He quoted di Donato to the effect that the plasma cell elements must be considered above all as an exponent of syphilitic specificity when their number is such that a true plasmomatous mass is constituted. Unna (cited by Hückel [12] and Ghon and Roman [24] and others), who was the first to use the expression plasmacytoma in 1891, described plasma cells as specific elements for lupus and other tuberculous processes of the skin. Since then, however, these cells have been found in other inflammatory reactions and in many normal organs.

In regard to our cases, we believe that the evidence that our first case was neoplastic is not convincing. The infiltration of leukocytes in the tumor itself is marked. Moreover, the plasma cells are more typical in appearance than those seen in the second case. The structure in all suggests an inflammatory rather than a neoplastic nature. It is true, however, that we have no proof of an etiologic agent. We were unable to employ the special stains used for the demonstration of micro-organisms. In the second case, we could find neither spirochetes nor tubercle bacilli. This, of course, of itself, does not rule out a syphilitic or tuberculous origin. The history and clinical signs do not, however, suggest such a causation of the lesions. The marked variation in size and shape of the plasma cells with the many giant forms, often multinucleated, we believe is evidence of a neoplastic nature. Aside

27. di Vestea, D.: Plasmoma tonsillare e angina sifilitica, Valsalva **4**:448, 1928.

from an occasional double nucleated plasma cell, we have not observed this great variation in inflammatory infiltration of the plasma cells. The fact that plasma cell tumors of the bone (multiple myeloma), which our second case somewhat resembles in histology, are probably malignant tumors, suggests that the localized growths are likewise at least neoplasms. It may be objected by some oncologists that the instances with apparent location of the tumor only in the mucous membranes, are really cases of multiple myeloma, in which the bony involvement has not been demonstrated by necropsy or thorough roentgen study. In our second case there was no roentgenologic evidence of bony involvement of the skull. In neither case were there clinical signs to suggest a bony involvement locally or elsewhere. It is extremely unlikely that a single metastatic growth in the mucosa of medullary origin could be present for at least two years without other clinical manifestations of the tumor process in the skeleton, viscera or elsewhere.

The localized nature, the general architecture and the cellular structure with absence of numerous mitotic figures indicate to us that the tumors in our second case should be classified as benign neoplasms of unknown etiology, to which the term "plasmacytoma" may be applied. The tumor in our first case had indefinite neoplastic characteristics and was probably inflammatory.

SUMMARY AND CONCLUSIONS

1. Twelve cases of plasma cell tumors occurring in the nasal or nasopharyngeal mucosa have been reported in the literature. We have reviewed these and added two cases of our own. Of these, all but two occurred in men.

2. Plasma cell tumors of the nasal and nasopharyngeal mucosa are probably much more frequent than the specific literature would lead one to believe. Undoubtedly many growths diagnosed clinically as nasal polyps and not studied microscopically have a predominant plasma cell structure.

3. Accumulations of plasma cells may accompany syphilitic, tuberculous or other chronic inflammatory processes to such a degree as to simulate true neoplasms.

4. Many of the plasma cell tumors are benign neoplasms. Most of the cases that appear malignant are probably manifestations of multiple myelomas.

OBSTRUCTIVE PULMONARY ATELECTASIS

FURTHER STUDIES *

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In a recent publication [1] on the subject of obstructive pulmonary atelectasis, two etiologic factors were described as being essential to its production, viz., bronchial obstruction and labored respiration or expiration against resistance. The latter of these two factors was contrary to the observations of Lee,[2] Coryllos and Birnbaum [3] and others,[4] who had produced the condition experimentally with regularity, and who believed a quiet, shallow respiratory cycle to be one of the important factors in its etiology. This idea has been carried down from the time of Pasteur [5] who, observing several cases of massive atelectasis associated with postdiphtheritic paralysis of the diaphragm, believed it due to a reduction in the depth of respiration.

When an attempt was made to reproduce the results of other investigators, the factor of straining respiration was accidently encountered and massive atelectasis produced with routine regularity in its presence.

That straining respiration was an essential factor in the production of massive atelectasis was made more evident, unfortunately, by several experiments [6] in which there was complete stenosis of a bronchus for a period of weeks or months under normal living conditions with no

* Submitted for publication, Nov. 21, 1930.

* From the Department of Surgery, University of Chicago.

* This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

* A preliminary report of this study was published in Proc. Soc. Exper. Biol. & Med. **27**:982, 1930.

1. Van Allen, C. M., and Adams, W. E.: The Mechanism of Obstructive Pulmonary Atelectasis, Surg. Gynec. Obst. **50**:385, 1930.

2. Lee, W. E.; Tucker, G.; Radvin, I. S., and Pendergrass, E. P.: Studies on Experimental Atelectasis, Ann. Surg. **88**:15, 1928; Experimental Atelectasis, Arch. Surg. **18**:242 (Jan.) 1929.

3. Coryllos, P. N., and Birnbaum, G. L.: Obstructive Massive Atelectasis of the Lung; Arch. Surg. **16**:501 (Feb.) 1928.

4. Henderson, Y.: The Physiology of Atelectasis, J. A. M. A. **93**:96 (July 13) 1929.

5. Pasteur, W.: Am. J. M. Sc. **100**:242, 1890.

6. Adams, W. E., and Livingstone, H. M.: Bronchial Injury and Repair, Ann. Surg. **91**:342, 1930.

resulting atelectasis. This appeared to be striking evidence that forced respiration was essential to the production of this condition. That this evidence was false will be brought out in the experiments to be described in this paper.

In more recent investigative work[7] dealing with the reparative processes of bronchi following injury, it was found that complete stenosis of a bronchus resulted from cauterization with a solution of silver nitrate. Much to our surprise, the total obstruction of the air passage was accompanied by massive atelectasis of the lobe of the lung. This was the stimulus for the following experimental work.

EXPERIMENTAL WORK

Our previous experiments entailed the use of an artificial obstruction to the air passages and proceeded in a manner by no means comparable to that in which massive atelectasis is produced clinically. The following experiments made use of an obstruction and mechanism that were entirely physiologic in the production of their results.

Dogs were used exclusively. Their weights ranged from 11 to 14 Kg. Morphine, 0.015 Gm. per kilogram of weight and atropine, 0.0004 Gm. per kilogram, were administered from one to one and one-half hours before bronchoscopy. No other form of anesthesia was employed. The experiments were terminated by electrocuting the animals,[8] thus avoiding agonal phenomena. The lungs were examined grossly, microscopically and roentgenologically.

The experiments were divided into three groups. The first two groups dealt with the location of the obstruction in the air passages. The third group had to do with the rôle played by respiration.

Typical protocols are as follows:

PROTOCOL 1 (dog 366 B).—*Obstruction located in the primary bronchus of a pulmonary lobe (obstructing the entire lobe).*

This animal was cauterized by the application of a 50 per cent solution of silver nitrate for ten seconds to the origin of the bronchus of the right middle lobe, and was killed two weeks later. Complete stenosis of the primary bronchus of the right middle lobe with 100 per cent atelectasis resulted.

Feb. 20, 1930: A prebronchoscopic dose of 0.15 Gm. of morphine and 0.004 Gm. of atropine was given by hypodermic injection. With the dog secured in a dorsal position and a gag inserted in its mouth, a bronchoscope was introduced and carried down to the right primary bronchus. The origin of the bronchus of the right middle lobe was located and a cotton applicator saturated with a 50 per cent

7. Adams, W. E., and Livingstone, H. M.: Further Studies in Bronchial Injury and Repair, to be published.

8. Hrdina, L. S.: Electrocution in Sacrificing Laboratory Animals, J. Lab. & Clin. Med. **15**:86, 1929.

solution of silver nitrate introduced into it and allowed to remain for ten seconds. After removal of the cautery, the bronchial wall appeared corroded. The dog was then placed in its cage, still in a stuporous state.

February 21: The dog was very quiet, appeared ill and did not eat. It did not cough or bark.

February 22: The dog appeared the same; however, an occasional nonproductive cough was noted.

February 23: The dog was much better. It ate some, but the cough was still present.

February 24: The dog appeared normal except for an occasional nonproductive cough.

February 25: There was no cough on this date.

February 27: The dog appeared healthy and normal.

March 5: Bronchoscopy was carried out as before. The origin of the bronchus of the right middle lobe was found to be completely stenosed.

March 6: The animal was electrocuted.

At autopsy, the bronchus of the right middle lobe was found to be completely stenosed over a distance of 0.75 cm. The right middle lobe was 100 per cent atelectatic. It was dark bluish red, flabby in consistency and would not float when placed in water (figs. 1 and 2). Microscopic sections verified the diagnosis made from the gross examination (figs. 3 and 4). The larger air passages were dilated and filled with a mucogelatinous substace, the retained secretions of the mucous glands. The smaller air passages were completely collapsed (figs. 5 and 6).

The results of thirty experiments comparable to protocol 1 were identical in every way. The number of applications of the cauterizing agent necessary to produce complete stenosis of the air passages varied from one to three, depending on the diameter of its lumen. Also the length of time consumed in producing complete stenosis varied from one to six weeks, depending on the diameter of the bronchus and also on the per cent of solution used in cauterization. A more detailed study of this will appear in a subsequent publication.[7]

If at autopsy the primary bronchus of a lobe was found to be completely stenosed, this condition was accompanied by massive atelectasis (100 per cent) of the obstructed pulmonary lobe. However, if the stenosis was all but complete, with an opening of only 1 mm. remaining, no atelectasis resulted. The lobe appeared normal both on gross and on microscopic examination.

PROTOCOL 2 (dog 213 B).—*Obstruction located in secondary bronchus of a pulmonary lobe (obstructing only a part of lobe; one-half or three-fourths).*

This animal was cauterized by the application of a 35 per cent solution of silver nitrate for ten seconds to the bronchus of the right lobe, just distal to the origin, and was killed two weeks later. Complete stenosis of only one of two main divisions of the primary bronchus of this lobe occurred, but no atelectasis resulted.

March 13, 1930: A prebronchoscopic dose of 0.15 Gm. of morphine and 0.005 Gm. of atropine was given by hypodermic injection. With the animal in a dorsal position with a gag inserted in its mouth, a bronchoscope was introduced and carried

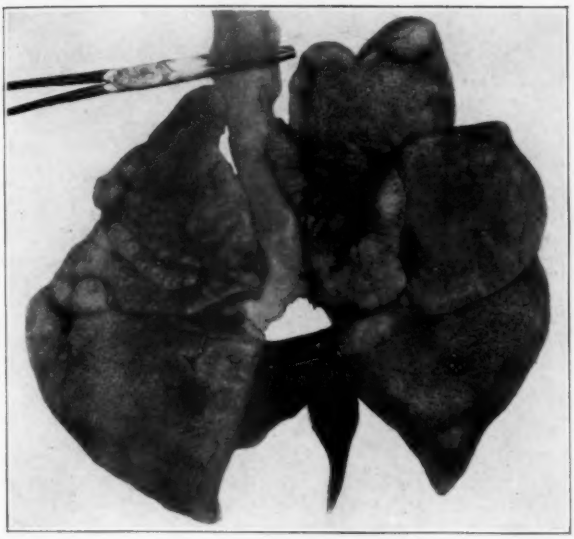

Fig. 1 (dog 486C).—Massive atelectasis of the accessory lobe of the lungs of one week's duration, following complete stenosis of the primary bronchus with 15 per cent solution of silver nitrate.

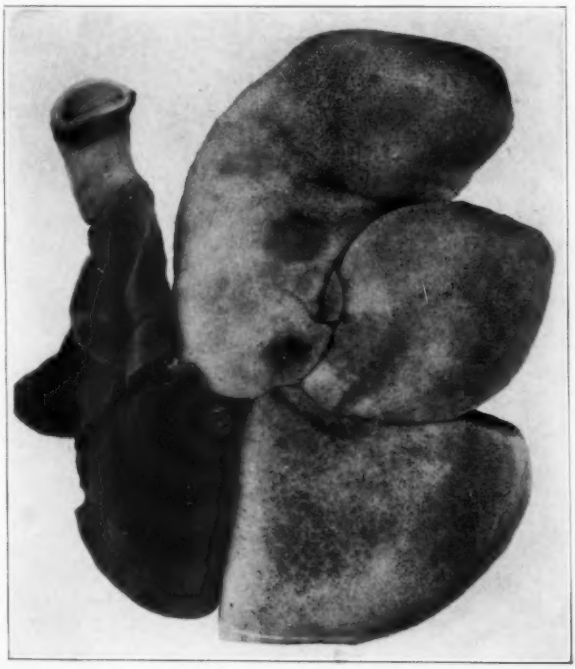

Fig. 2 (dog 641C).—Massive atelectasis of entire left lung of two weeks' duration, following complete stenosis of the left primary bronchus with 35 per cent solution of silver nitrate.

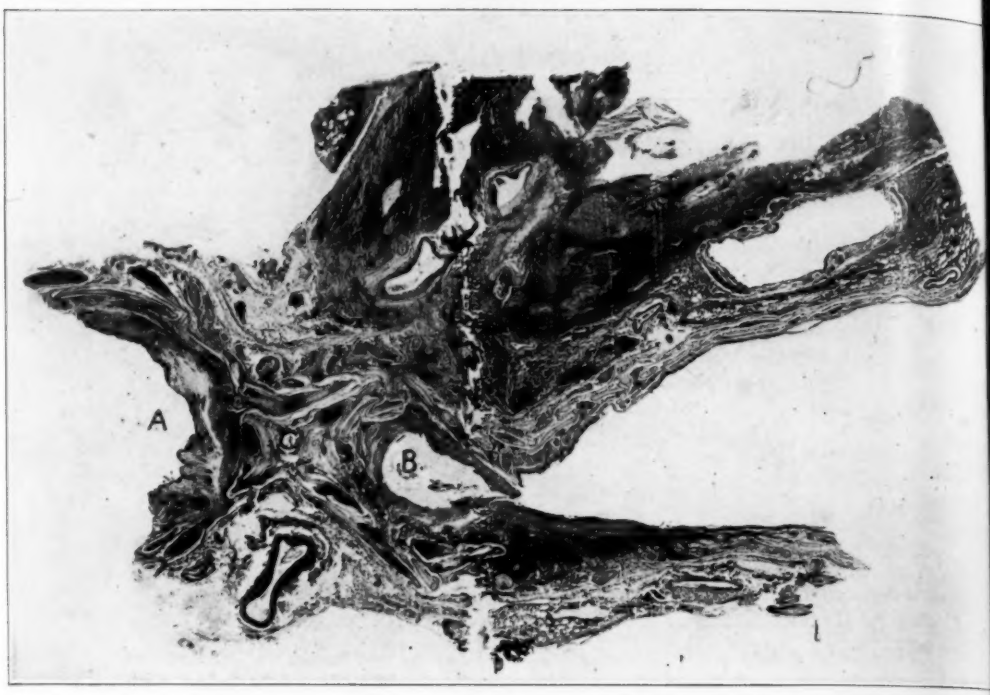

Fig. 3 (dog 365B).—Microscopic appearance of stenosed primary bronchus of a pulmonary lobe tw
weeks following cauterization with 50 per cent solution of silver nitrate. *A* indicates the origin of th
primary bronchus of the lobe and the proximal side of the stenosis; *B*, the distal side of the stenos
Reduced from a magnification of × 7.

Fig. 4 (Dog 365B).—Higher magnification of the area indicated by *C* in figure 3. Note the partial
destroyed cartilage plates intermingled with fibrous tissue, with complete regeneration of the bronch
epithelium on either side of the stenosis. Reduced from a magnification of × 30.

to the right primary bronchus. The origin of the bronchus of the right lower lobe was located, and a cotton applicator saturated with a 35 per cent solution of silver nitrate was introduced into it to the level of division of the primary into the several secondary bronchi. It was allowed to remain for ten seconds. After removal of the cautery, the bronchial wall appeared encircled by an area of corrosion. The dog was then placed in its kennel, still in a drowsy condition.

March 14: The dog was quiet. It did not eat or bark, and appeared somewhat ill, but would walk around.

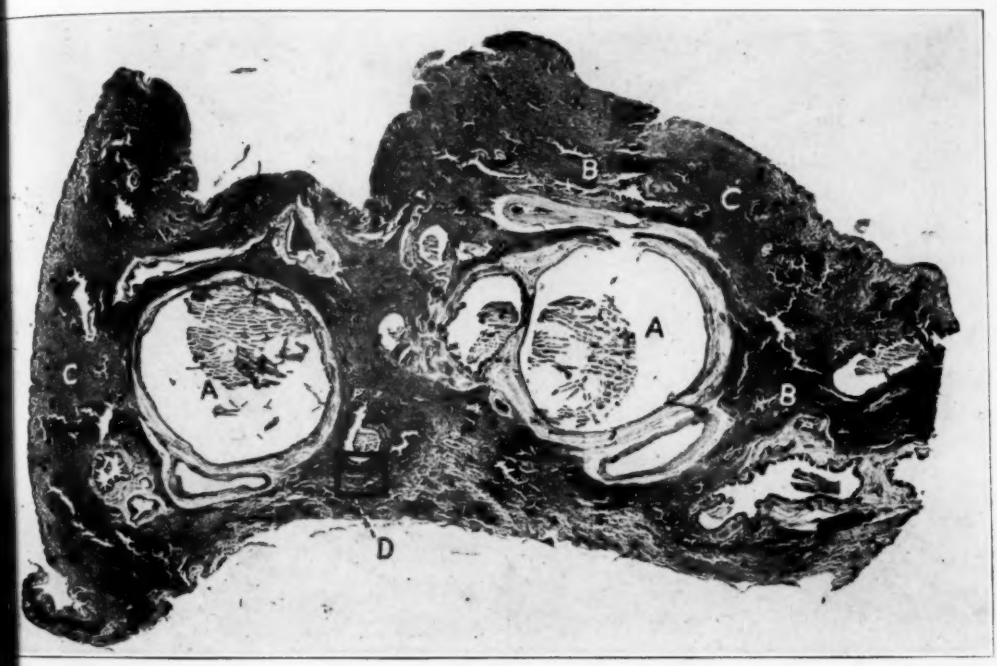

Fig. 5 (dog 365B).—Microscopic appearance of an atelectatic lung distal to a completely stenosed primary bronchus of three weeks' duration following cauterization which was done with 50 per cent solution of silver nitrate. *A* shows the dilated larger air passages filled with mucoid material (this entirely filled the lumen of the air passages before fixation); *B*, collapsed smaller air passages, and *C*, atelectatic parenchyma. Reduced from a magnification of × 9.

March 15: There was little change in the animal's condition.

March 16: A nonproductive cough was occasionally noted. The dog ate some food, but was quiet.

March 17: The dog was very well except for an occasional nonproductive cough.

March 18: A slight cough was present.

March 20: The dog appeared healthy and normal.

March 26: Bronchoscopy was repeated. The primary bronchus of the right lower lobe presented an opening about 1 or 2 mm. in diameter.

March 26: The dog was electrocuted.

At autopsy, the lateral secondary bronchus to the lower right lobe was completely stenosed, with the air passages distal to the stenosis dilated and filled with a mucogelatinous material, the retained secretion from the mucous glands. The medial secondary bronchus was markedly but not completely stenosed, an opening of 1 or 2 mm. remaining. There was no dilatation distal to this incomplete stenosis. The entire lobe was normally air-containing on external examination and on cut

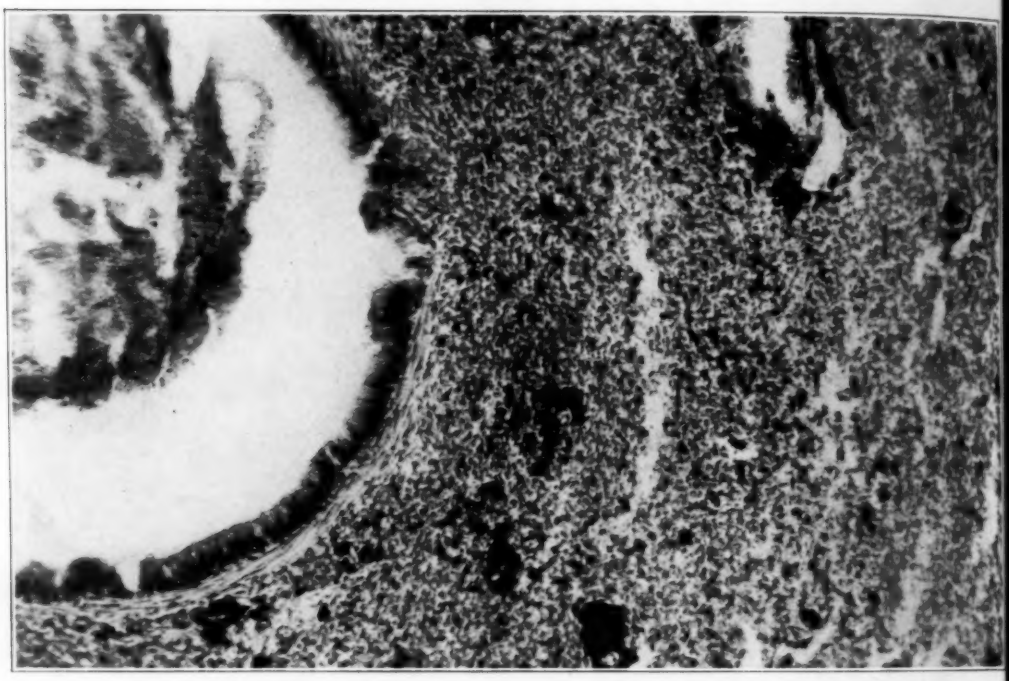

Fig. 6 (dog 365B).—Higher magnification of area indicated by *D* in figure 5. Note the dilated bronchus surrounded by atelectatic parenchyma and filled with mucoid material. Reduced from a magnification of × 175.

section. Pieces floated on the surface when placed in water. Microscopic section showed the alveoli to be air-containing (figs. 7, 8 and 9).

The same results were obtained in ten experiments, protocol 2 being typical of this series. Various lobes of the lungs were used, like results being obtained with regularity. The duration of the experiments was also varied from two weeks to two months with no alteration in the end-results. Thus, complete obstruction to the air passages of only a part of a lobe was not followed by massive collapse. Only a dilatation of the larger air passages distal to the stenosis resulted, with the alveoli normally air-containing.

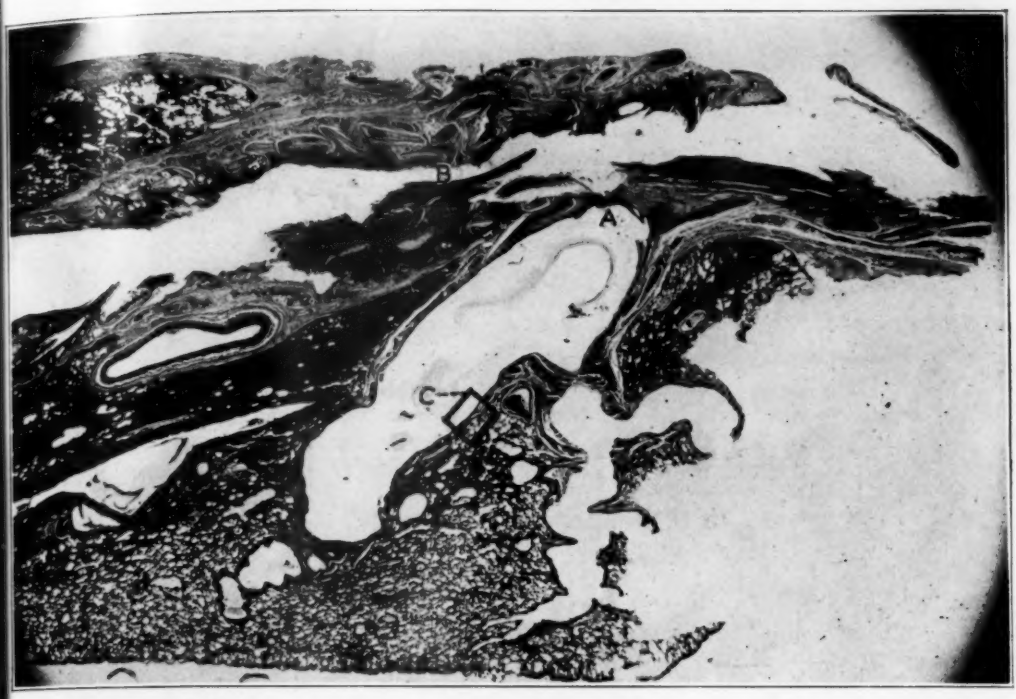

Fig. 7 (dog 213B).—Microscopic appearance of complete stenosis of secondary bronchus of a lobe of the lung and partial stenosis of remainder of air passage two weeks following cauterization with 35 per cent solution of silver nitrate. *A* shows complete stenosis with dilatation of air passage distal to the stenosis. Reduced from a magnification of × 6.

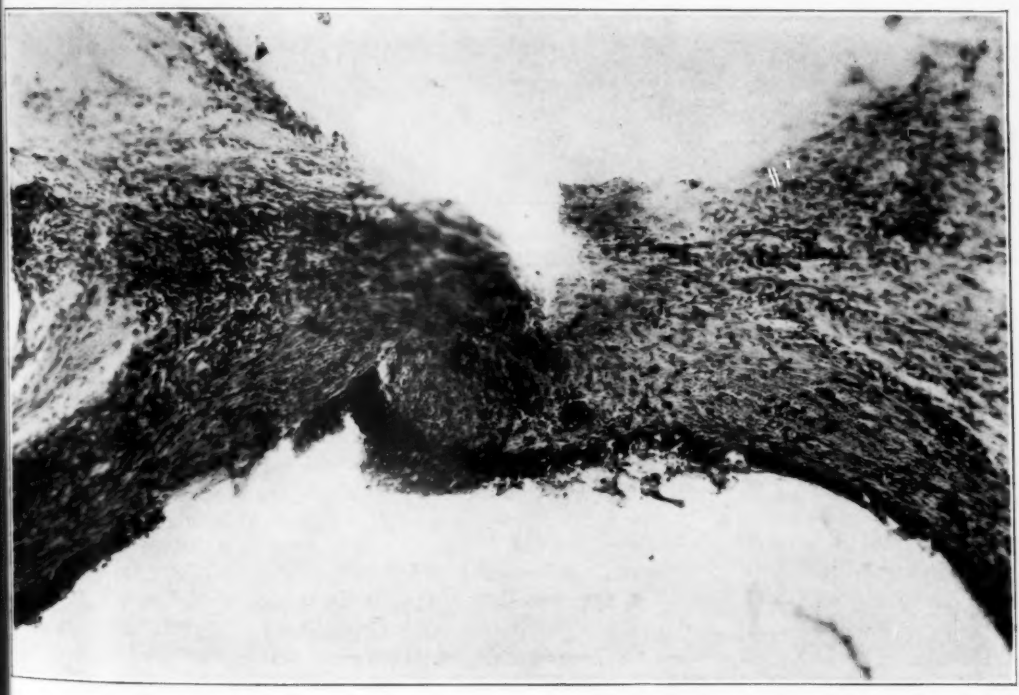

Fig. 8 (dog 213B).—Higher magnification of area *A* in figure 7 showing fibrous tissue septum and regenerated bronchial epithelium on distal side of stenosis. Reduced from a magnification of × 120.

The factor of respiration in the production of massive atelectasis has been greatly discussed by the many writers on this subject. The following six experiments were carried out to determine if a certain type of respiration was essential to the production of this condition.

PROTOCOL 3 (dog 661 C).—*Total obstruction of an entire pulmonary lobe in the presence of normal respiration.*

This dog was cauterized by the application of a 35 per cent solution of silver nitrate for ten seconds to the origin of the bronchus of the accessory lobe, and

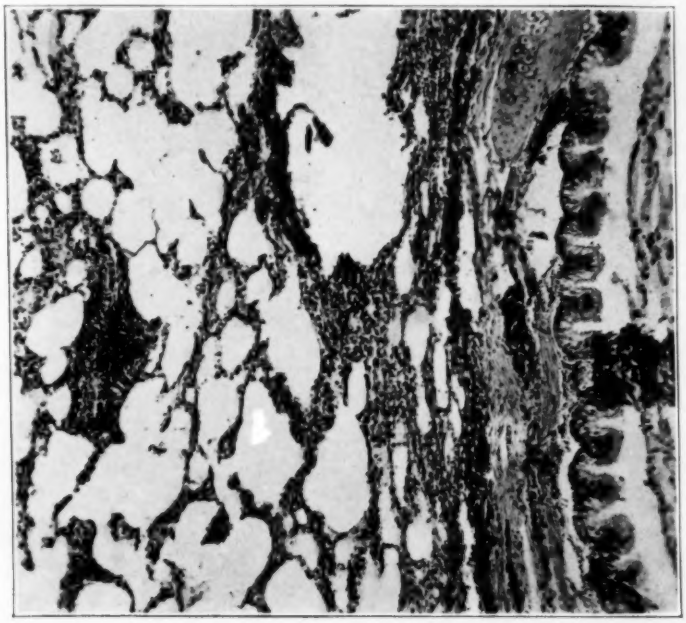

Fig. 9 (dog 213B).—Higher magnification of area *C* in figure 7 showing dilated bronchus surrounded by normally inflated alveoli. Reduced from a magnification of × 85.

killed two weeks later. Complete stenosis of the primary bronchus of the accessory lobe with 100 per cent atelectasis of this lobe resulted.

May 20: A prebronchoscopic dose of 0.15 Gm. of morphine and 0.004 Gm. of atropine was given by hypodermic injection. With the dog lying in a dorsal position and a gag inserted in its mouth, a bronchoscope was introduced and carried down to the right primary bronchus. The origin of the bronchus of the accessory lobe was located and a cotton applicator saturated with 35 per cent solution of silver nitrate introduced into it and allowed to remain for ten seconds. After removal of the cautery, the bronchial wall presented an area of corrosion encircling the lumen. The dog was then placed in its kennel in a stuporous condition.

May 21, 1930: The animal was very quiet, appeared ill and refused food.

May 22: An occasional nonproductive cough was noted. The dog appeared ill, refused food and was quiet.

May 23: The dog was somewhat better, but was still quiet. It ate little, and the cough was still present.

May 24: The cough was still present; otherwise the dog was quite well. Its appetite was good.

May 25: The dog coughed less frequently, and seemed quite well.

May 27: The dog appeared healthy and normal.

June 10: The animal was electrocuted. (No bronchoscopy was done prior to electrocution.)

At autopsy, the primary bronchus of the accessory lobe was found completely stenosed for a distance of 0.75 cm. The accessory lobe was found to be 100 per cent atelectatic. It was bluish red and of the consistency of flabby muscle, and pieces sank readily when placed in water. The larger air passages were dilated and filled with a mucogelatinous material, the retained secretions of the bronchial mucous glands. The smaller air passages were completely collapsed. Microscopic sections verified the diagnosis made from the gross examinations.

Protocol 3 is typical of the six experiments of this type, similar results being obtained in each. Thus, a particular type of respiration is unessential for the production of massive collapse, as it occurs in the presence of normal respiration.

The association of massive collapse and pneumonia has recently received much attention.[9] It is the opinion of some[10] that massive atelectasis is a precursor of pneumonia in a large percentage of cases.

In some recent investigative work,[11] it was found that the parenchyma of the lung of normal dogs was always infected with bacteria. In several of the foregoing experiments cultures were taken of the collapsed parenchyma of the lung. In each case the same organisms were cultivated as those found in the parenchyma of the lung of a normal dog. However, in no case of massive atelectasis was there associated any form of pulmonary suppuration. The pathogenicity of these organisms is being investigated at the present time.

COMMENT

It has been generally accepted among recent workers that the production of massive atelectasis is favored by the presence of a diminished respiratory effect. It is contended that this form of respiration leads to the collection and accumulation of secretions within the air passages.

9. Coryllos, P. N.: Postoperative Aponeumatosis and Postoperative Pneumonia, J. A. M. A. **93**:98 (July 13) 1929; Postoperative Pulmonary Complications and Bronchial Obstructions, Surg. Gynec. Obst. **50**:795, 1930.

10. Coryllos, P. N., and Birnbaum, G. L.: Lobar Pneumonia Considered as Pneumococcic Lobar Atelectasis of the Lung: Bronchoscopic Investigation, Arch. Surg. **18**:190 (Jan.) 1929. Henderson, Y.: Acapnia as a Factor in Post-Operative Shock, Atelectasis and Pneumonia, J. A. M. A. **95**:572 (Aug. 23) 1930.

11. Livingstone, H. M., and Adams, W. E.: Bacterial Flora of the Lower Respiratory System of Normal Dogs, J. Infect. Dis. **48**:282 (March) 1931.

Thus with obstruction, atelectasis is produced by absorption of the imprisoned air by the blood. In our former experiments it appeared impossible to produce this picture in the presence of quiet respiration. However, an artificial means of obstruction was used, and experiments ran for only twenty-four hours or less. Our belief that a forced respiratory effort was an essential factor was unfortunately strengthened by several experiments in which the air passage to part of a lung was completely obstructed without resultant atelectasis. A like result has been described in a number of experiments. Thus, when the obstruction in the lung is located in such a manner that all of the lobe is affected, complete

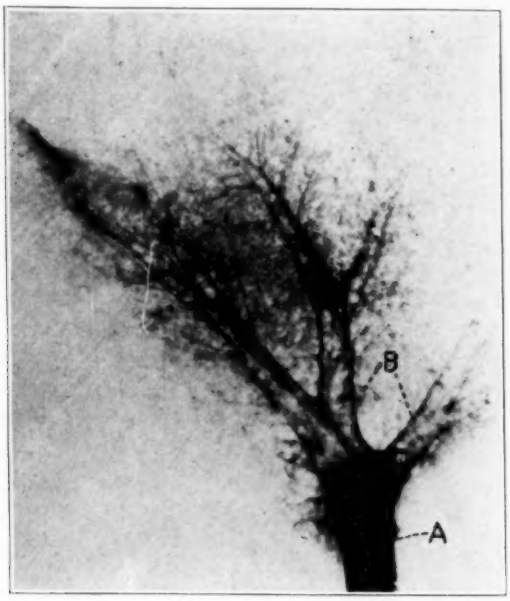

Fig. 10.—Roentgenogram of a dog's pulmonary lobe, to illustrate various locations in the air passages at which stenosis was produced. *A* shows the primary bronchus of the lobe of the lung, and *B*, the secondary bronchus.

atelectasis follows. However, if a small amount of the lobe (one-third, one-fifth, etc.) is left unobstructed, no atelectasis is produced (fig. 10).

It is the general belief that the lobules of a lobe of the lung are each a closed system in themselves. That is, there are no communications between the air passages of two or more adjacent lobules of a lobe. Indeed, the anatomy of the lung has been carefully studied by dissection under microscopic vision, resulting in the foregoing conclusion.[12] How-

12. Macklin, C. C.: The Musculature of the Bronchi and Lungs, Physiol. Rev. **9**:1, 1929. Reisseisen, F. D.: Ueber den Bau der Lungen, Berlin, 1822. Miller, W. S.: Anastomosing Bronchi in Human Lung, Arch. Path. **3**:161 (Feb.) 1927.

Fig. 11 (dog 610B).—Roentgenogram of the chest two weeks following cauterization of the right primary bronchus with 35 per cent solution of silver nitrate. Note the heart is drawn over against the right lower thoracic wall. (Autopsy showed massive atelectasis of entire right lung similar in appearance to that shown in figure 2.) Note the markings for the relative position of the heart and the left lung.

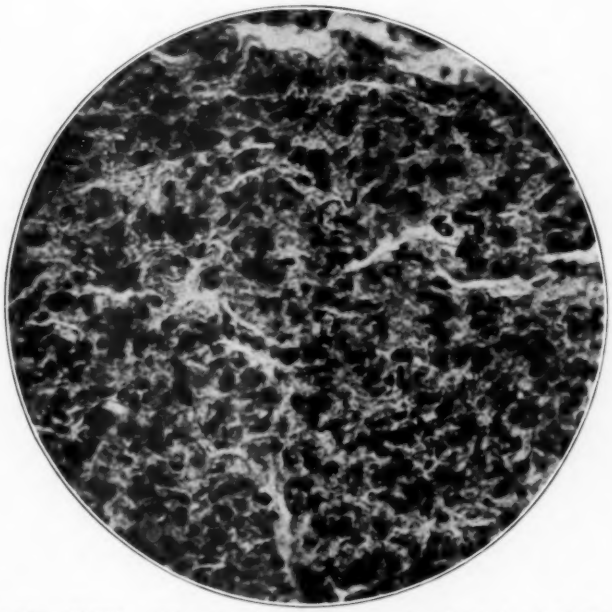

Fig. 12 (dog 610B).—Microscopic appearance of atelectatic right lung showing complete collapse of the alveoli; × 450.

ever, in view of these experiments it appears probable that there are communications between the alveoli of the many lobules of a lobe of the lung. The obstructed portion of the lung is evidently retained in the inflated condition by air passing this portal of entry, which explains why collapse is not obtained when a part of the lobe is left unobstructed.

In the third group of experiments an attempt was made to eliminate all factors that might produce a forced respiratory effort. Massive atelectasis was always produced in the presence of normal respiration. That diminished respiratory excursion causes an accumulation of secretion in the air passages is still a debatable question. Many postoperative neurosurgical patients exhibit a shallow, effortless type of respiration for many hours, with seldom the production of massive atelectasis or pneumonia. Also, it is not uncommon to see massive atelectasis in patients with a respiratory excursion of normal range.

Clinical cases of obstructive pulmonary atelectasis may perhaps be divided into two groups according to the rate of production. Although as yet there has been no direct evidence of valvular obstruction producing massive atelectasis clinically, it appears likely that cases occurring within a few minutes [13] after obstruction do so by means of a check-valve arrangement similar to that described in a former communication.[1] There is another group of patients in which the condition develops slowly, over a period of hours. This is comparable to the rate at which atelectasis was produced in the foregoing experiments, which were controlled both bronchoscopically and roentgenologically.

CONCLUSIONS

1. Complete obstruction of the air passages of an entire pulmonary lobe was essential to the production of massive atelectasis.

2. Complete obstruction of the air passages of part of a lobe was not accompanied by atelectasis of the obstructed part.

3. No particular form of respiration was essential to the production of massive collapse. (The rate of production may be increased by a valvular obstruction and a straining type of respiration.)

4. Communications appeared to be present between the alveoli of adjacent lobules of a pulmonary lobe in dogs.

5. Pulmonary suppuration was not associated with obstructive pulmonary atelectasis produced experimentally in dogs.

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13. Bergamini and Sheppard: Ann. Surg. **86**:35, 1927. Lilienthal, in discussion on Leep, W. E.; Ravdin, I. S.; Tucker, G., and Pendergrass, E.: Experimental Atelectasis, Arch. Surg. **18**:242 (Jan.) 1929.

CALCIFICATION IN THE SUBCUTANEOUS TISSUES

REPORT OF A CASE ASSOCIATED WITH CHRONIC ATROPHIC ARTHRITIS *

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A brief résumé of the various theories advanced to explain the formation of the deposits of calcium or calcification follows.

Pauli and Samec [1] showed that in a colloidal albuminous solution, calcium carbonate and calcium phosphate are many times more soluble than in water. These salts could therefore be carried in the blood in nearly the same form as they are found in the deposits.

Holt, La Mer and Chown [2] demonstrated that blood serum is normally saturated up to 200 per cent with neutral calcium phosphate, and that this salt will remain for days without precipitating. They thought, however, that most of the calcium is carried in the form of the much more readily soluble acid carbonate and acid phosphates which may be changed into the neutral salts by the loss of carbon dioxide.

Barille [3] held that calcium is contained in the blood as a double salt, calcium carbonophosphate, unstable and soluble only in the normal concentration of carbon dioxide in the blood. If the carbon dioxide is reduced locally, this unstable double salt breaks down into its two constituents which are then converted into the neutral carbonate and neutral phosphate in the proportion in which these salts are found in bone.

Wells [4] found that this proportion by weight is 15 parts of calcium carbonate to 85 parts of calcium phosphate, i. e., in the proportion of 1 molecule of carbonate to 3 of phosphate. In pathologic calcification, he found these two salts in the same proportion.

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* Submitted for publication, Dec. 5, 1930.

1. Pauli, W., and Samec, M.: Ueber Löslichkeitsbeeinflussung von Electrolyten durch Eweisskorper, Biochem. Ztschr. **17**:235, 1909.

2. Holt, L. E.; La Mer, V. K., and Chown, H. B.: Studies in Calcification: I, II and III, J. Biol. Chem. **64**:509, 1925.

3. Barille, A.: De l'action de l'acide carbonique sous pression sur les phosphates metalliques; combinasion (carbonophosphates) ou dissolution, applications diversés, J. de pharm. et chim. (series 6) **19**:14, 71, 196, 245 and 295, 1904; (series 7) **1**:342, 1910.

4. Wells, H. G.: Pathologic Calcification, J. M. Research **9**:491, 1906: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1918.

Barille [3] and Wells [4] explained pathologic calcification because of the supposition that the blood and tissues hold their calcium salts in solution only because of a fixed content of carbon dioxide in the same solution. When the amount of carbon dioxide is decreased beyond a certain point, the salts precipitate. In places of low grade activity, the content of carbon dioxide would probably be low. Such situations would exist in areas of necrosis or fibrosis, thrombosed vessels or hematomas and the colloid in the thyroid gland.

Klotz [5] explained calcification in certain areas of necrosis as follows: Fatty acids form in the necrotic tissues and react with soluble sodium and potassium salts in the blood and tissues to form soaps. Soluble calcium salts react with the soaps to form insoluble calcium soaps which are precipitated. By the constant exposure of the soaps to the influence of carbonate and phosphates in the body fluids, a gradual conversion of the calcium soaps into calcium carbonate and phosphate occurs.

Watt [6] and others could find no evidence that cellular activity played a part in the formation of deposits of calcium.

REPORT OF CASE

History.—Mrs. S. C., aged 63, a widow, a housekeeper, was born in Canada and spent her entire adult life in various parts of the United States. She was referred in October, 1929, by Dr. Carl B. Davis of Chicago, because of tender nodules beneath the skin of the buttocks, the hips and the left forearm.

In 1915, she was seen by Dr. E. E. Irons of Chicago, at which time she had a maxillary sinusitis, a number of retinal hemorrhages, a high grade secondary anemia and chronic arthritis. Her blood pressure was 115 systolic and 70 diastolic; the urine was normal; the Wassermann reaction of the blood was negative. She then had treatments for the sinusitis, and several abscessed teeth were removed.

Early in 1920 she first noticed some tender lumps in the left buttock, which at times were painful. On Aug. 21, 1920, Dr. James I. Case of Battle Creek Sanitarium excised one for diagnosis.

The pathologic report by Dr. A. S. Warthin was as follows:

When cut open, the mass appeared to be more or less tubular. The interior of these tubes contained a white semiliquid material. Microscopic examination showed masses of deposits of lime salt surrounded by trabeculae of dense connective tissue. The deposits were in areas suggestive of fat lobules. They were the so-called "fat-stones," calcification following the necrosis of fat. There were also areas of old hemorrhage showing foreign body cells and phagocytes containing hemosiderin. This could probably be explained by some old traumatic injury.

The diagnosis was calcification following the necrosis of fat.

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5. Klotz, O.: Studies upon Calcareous Degeneration, J. Exper. Med. **7**:633, 1905; On the Presence of Soaps in the Organism in Certain Pathological Conditions, Am. J. Physiol. **13**:21, 1905.

6. Watt, J. C.: The Deposition of Calcium Phosphates and Calcium Carbonate in Bone and in Areas of Calcification, Arch. Surg. **10**:983 (May) 1925; The Deposition of Calcium Salts in Areas of Calcification, ibid. **15**:89 (July) 1927.

Fig. 1.—The subcutaneous nodules over the left iliac fossa.

Fig. 2.—The nodule at the site of the blow over the left ulna.

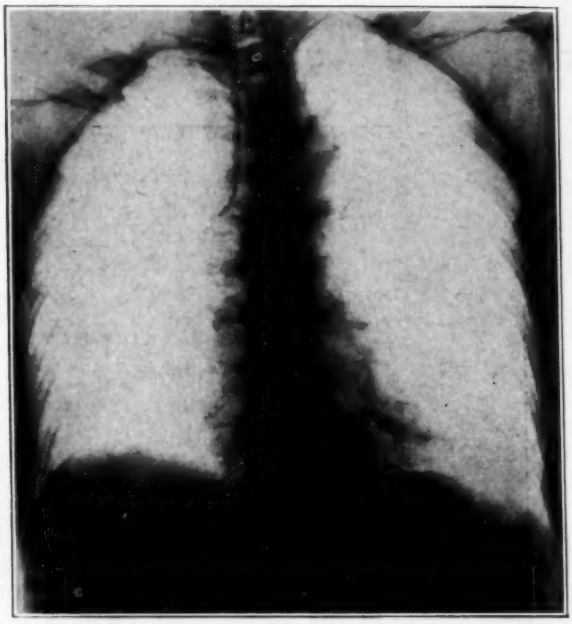

Fig. 3.—The thoracic spine, which shows an atrophic arthritis with some destruction of the vertebral bodies.

Fig. 4.—Roentgenogram of the nodules over the left iliac fossa.

During the following four years, similar tender lumps appeared over the right hip and in the right buttock in the region of the ischial tuberosity. These were excised by Dr. Carl B. Davis on May 7, 1924.

The pathologic report from the laboratory of the Presbyterian Hospital, Chicago, was as follows:

Macroscopic Examination.—The tissue consisted of two masses, each containing a rather large, hard, firm nodule, about which was a cluster of smaller nodules. One large nodule was adherent to the skin. On cut section, there was a thick, whitish substance resembling white lead which oozed out.

Microscopic Examination.—There were many well defined areas containing an opaque and granular substance. These were surrounded by a dense fibrous connective tissue. In a few areas the granular substance resembled crystals.

Fig. 5.—Roentgenogram, showing the two groups of nodules in the buttocks. The femoral arteries are markedly calcified.

The diagnosis was subcutaneous calcification.

The patient was admitted to St. Luke's Hospital on Oct. 24, 1929. Since her discharge from the Presbyterian Hospital, similar tender nodules had appeared over the left hip, and those on the left buttock had increased in number and size. She had struck her left forearm, and a permanent tender swelling appeared at the site of the injury. The arthritis and the severe anemia had never shown any improvement. The fourth toe on the left foot had developed into a severe grade of hammer toe.

Physical Examination.—Physical examination showed an anemic, poorly nourished white woman. The skin was very dry and in areas, particularly over the cubital fossae, had the appearance of containing a white chalky deposit. Over the

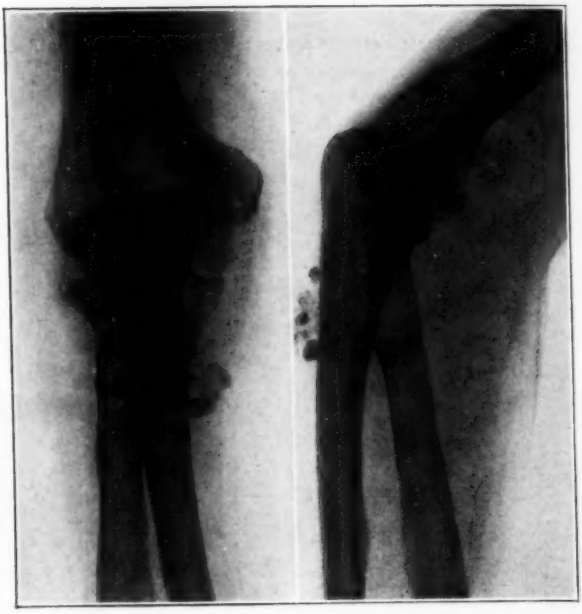

Fig. 6.—Roentgenogram of the nodule over the left ulna. The arrangement of the calcification in the nodule is shown better here than in the other figures.

Fig. 7.—The pelvis and the buttocks after removal of the nodules.

left iliac fossa and posteriorly in the left buttock were small, irregular, hard, movable masses. They varied in size from that of a pea to that of a walnut. Some were adherent to the skin, and others could be moved freely beneath the skin. There was a more superficial nodule on the dorsal aspect of the left forearm. The fourth toe of the left foot showed a severe grade of hammer toe. All of the joints of the hands and feet were nodular and limited in motion.

Laboratory Examination.—The blood count showed: hemoglobin, 57; red cells, 2,900,000; white cells, 5,400; polymorphonuclear leukocytes, 52, and lymphocytes, 48. The morphology of the red blood cells was normal, except for a slight poikilocytosis. The Wassermann reaction was negative.

Chemical analysis of the blood showed: urea nitrogen, 10 mg.; sugar, 100 mg.; uric acid, 2.8 mg.; plasma chlorides, 6.5 mg., and calcium, 11.8 mg. per hundred cubic centimeters of blood. The coagulation time was two minutes.

The urine was normal, except for a few pus cells.

The basal metabolic rate was —12 per cent.

Roentgen Examination.—Films of the pelvis, taken on October 25, showed deposits of calcium in the region of the left hip about half way between the crest of the ilium and the greater trochanter. This calcified mass of bodies appeared to be in the soft tissues. There was also calcification in the soft tissues in the area of the buttocks, especially on the left.

Two inches beyond the left elbow was a cluster of calcified bodies in the soft tissues. The joints, particularly of the hands, feet and spine, showed a marked atrophic arthritis.

There was generalized calcification in the walls of the arteries. The fields of the lungs appeared clear. Examination of the nasal accessory sinuses showed them to be fairly clear throughout. There was a slight thickening in the region of the right ethmoid.

Operation.—On October 26, with the patient under general spinal anesthesia and local anesthesia in the arm, all of the palpable nodules were excised. The hammer toe was amputated. When cut, the skin gave a marked grating sensation. The nodules were found to be in the subcutaneous fat. Those over the hip were adherent to the fascia lata.

Pathologic Examination (by Dr. Leila C. Knox).—Macroscopic Examination: The specimen consisted of six pieces of tissue from the arm, buttock and iliac region and a hammer toe. The latter showed no lesions, except the angulation at the interphalangeal joint and a callosity of the dorsal side. The other fragments varied in size, the largest being 7 by 6 by 3 cm., with an area of normal skin. The masses were very hard and consisted of about half fat; the rest was a solid grayish tissue in which were many calcified yellowish areas.

Microscopic Examination: Sections of the tissue showed fibrous trabeculae nearly filled with amorphous and crystalline material. Most of it was calcified. There was no formation of bone and no cellular tissue. These areas were surrounded by a few fibroblasts or hyaline fibrous material from the subcutaneous fascia. Occasionally there were considerable numbers of foreign body giant cells surrounding the smaller calcified nodules.

Chemically, this substance consisted mostly of the salts of calcium with small amounts of magnesium and traces of other metallic substances.

There was no tumor or tuberculosis.

Diagnosis.—The diagnosis was calcified nodules in the subcutaneous fat of the arm and the buttocks; hammer toe.

SUMMARY

A case showing peculiar areas of calcification in the subcutaneous tissues is reported. The appearance of the skin and the grating sensation when it was cut would appear to indicate the presence of a fine deposit of calcium in the skin also.

Although the majority of the deposits showed a bilateral symmetry, their locations were such that trauma could be the etiologic factor in producing conditions that favor calcification. The deposit on the forearm followed a definite and severe blow in the exact location. The buttocks over the ischial tuberosities and the areas above the greater trochanters receive constant trauma, particularly in a very thin person, as was the patient in the case reported.

It is of interest that this condition should be found in a patient with a marked atrophic type of chronic arthritis. The density of the bones is much decreased, even though the skin and subcutaneous tissues contain deposits of calcium. The chemical composition of the blood and the basal metabolism do not appear to have any relation to the local condition, unless the low basal metabolic rate and anemia give a low carbon dioxide content in the tissues. Conditions favorable to a deposit of calcium salts would then be much more readily created.

The severe grade of anemia is probably a part of the long-standing arthritis.

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FORTY-FIFTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY*

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CONGENITAL DEFORMITIES

Congenital Dislocation of the Hip.—Evans [1] reexamined twenty-five of seventy patients with congenital dislocation of the hip whom he had treated between 1903 and 1920. He found one bad, two poor, thirteen good and nine perfect results, using function as a criterion. Roentgen examination showed that of the thirty-two hips reduced, there were three anterior transpositions, five eccentric nearthroses, sixteen concentric reductions and eight normal hips. The treatment in these cases was closed reduction, followed by prolonged fixation in one position (90 degrees of flexion, 70 degrees of abduction, 0 degrees of rotation) for a period varying from one to eighteen months. Evans allowed walking at once with a 6-inch (15.24 cm.) patten, but after removal of the plaster, the child was kept recumbent for three months and allowed

* This Report of Progress is based on a review of 163 articles selected from 393 titles dealing with orthopedic surgery appearing in the medical literature between Jan. 1, 1931, and April 4, 1931, supplemented by a few articles of older date. Only those papers that seem to represent progress have been selected for review.

1. Evans, E. L.: Brit. M. J. **2**:1035 (Dec. 20) 1930.

to kick about in bed by day and held splinted in the old position by night. For three months after walking had recommenced, a patten of 1½ inches (3.77 cm.) was worn on the sound side to hold the affected leg abducted.

Kidner [2] stated that the tightly stretched and thickened capsule was the chief obstruction in reducing congenital dislocation of the hip in children under 10. He advised in such cases incising the capsule in a longitudinal plane, freeing particularly the adhesion of the capsule from the side of the ilium, in this way exposing the true acetabulum. After this was done he found that reduction of the dislocation was relatively easy, and that the position was maintained without great difficulty.

GROWTH DISTURBANCES OF BONE

Köhler's Disease.—Sauer [3] found Köhler's disease of frequent occurrence without symptoms. The condition was often found in roentgenograms of the feet, which were taken for other diseases. He believed that it was produced by the presence of more than one center of ossification in the scaphoid bone. One case was followed in which there were two centers of ossification which later developed into typical Köhler's disease.

[ED. NOTE.—The evidence produced is not sufficient to convince us that multiple centers of ossification in the scaphoid bone are the necessary cause of Köhler's disease.]

Infantile Patella.—Mau [4] described changes in roentgenograms of the patellae of children, which resembled the growth disturbances seen in many other epiphyses. In severe cases there was an apparent partial necrosis of the patella. The subjective symptoms were very mild. Prognosis was excellent in most cases. The author believed that the condition was an aseptic necrosis due to abnormal strain or pressure.

RICKETS AND DISTURBANCES OF CALCIUM METABOLISM

Rickets.—Holmes [5] voiced the opinion that vitamin D and viosterol were not identical substances. He reviewed the clinical and laboratory studies on the antirachitic properties of vitamin D found in cod liver oil and compared it with that of viosterol. The data that he gathered suggested that in the treament for rickets either vitamin D as it occurred in cod liver oil possessed properties not present in viosterol, or that vitamin A or some other substance in cod liver oil enhanced the antirachitic vita-

2. Kidner, F. C.: J. Bone & Joint Surg. **13**:104, 1931.
3. Sauer, W.: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:679, 1929.
4. Mau, C.: Deutsche Ztschr. f. Chir. **288**:1, 1930.
5. Holmes, A. D.: New England J. Med. **204**:211, 1931.

min so that it became more effective in the treatment for rickets than equivalent units of viosterol.

Compere [6] studied the roentgen changes and the chemical reactions in the blood in ten rachitic infants and one nonrachitic patient and found that administration of cod liver oil with phosphorus was more effective in healing rickets than was administration of cod liver oil alone. When such patients were placed in ideal antirachitic surroundings and also given cod liver oil in doses of 3 to 6 teaspoonfuls daily with phosphorus, the calcium and phosphorus in the blood increased rapidly, and the healing process in the bone as shown by a roentgenogram progressed very rapidly. Phosphorus when given alone had little effect on the calcium and phosphorus content of the blood unless there had been previous stimulation by ultraviolet irradiation or the administration of cod liver oil.

Bunker and Harris [7] studied the antirachitic protective action of various portions of the light spectrum. Rats were given the Steenbock rachitic diet, and were exposed to mercury vapor lamps of standardized voltage and distance. They found that the light given by the lamp gave uniform protection, but that if it was followed by exposure to the infra-red portion of the spectrum alone, only one third of the animals were protected. If the infra-red exposure preceded the exposure to the entire spectrum from the lamp, two thirds of the animals were protected against rickets. Exposure to infra-red alone gave no protection. Where all light below 3,000 angstrom units was filtered out and infra-red was present, 23 per cent of the animals were protected. If all light below 3,000 angstrom units plus the infra-red was filtered out, 43 per cent of the rats were protected.

Calcium in the Healing of Fractures.—Speed [8] concluded from his studies on dogs and in a series of consecutive cases in human beings that the diminution of the calcium-phosphorus ratio in the blood had little or nothing to do with the rate of healing of fractures, and that such determinations offered little in helping determine a prognosis as to the speed of union.

Osteitis Fibrosa.—Hunter [9] reported a case of osteitis fibrosa in a 37 year old woman, who was treated by parathyroidectomy. There was marked improvement following the operation with increase in weight, disappearance of pain and restoration of menstruation. The bony

6. Compere, E. L.: Effect of Phosphorus on Rickets: Roentgenologic Changes in Rickets Following Administration of Phosphorus, Am. J. Dis. Child. **40**:1177 (Nov.) 1930.

7. Bunker, J. W. M., and Harris, R. S.: Am. J. Pub. Health **20**:1287, 1930.

8. Speed, K.: J. Bone & Joint Surg. **13**:58, 1931.

9. Hunter, D.: Proc. Roy. Soc. Med. (Clin. Sect.) **24**:40, 1930-1931.

tumors (osteoclastomas) gradually disappeared, although by roentgen examination the bone density remained the same. Tetany followed operation and lasted seventeen days. Parathyroid extract-Collip was given from the sixth to the twenty-sixth day. The serum calcium, which before operation was about 12 mg. per hundred cubic centimeters, dropped to about 9 mg.; the plasma phosphorus was unchanged. The excretion of calcium, although considerably lower after operation, still remained higher than the intake of calcium five months after the operation. The histologic appearance of the parathyroid suggested hyperplasia and exceptional functional activity rather than an autonomous neoplasm. The bone tumors could not be differentiated from the giant cell tumors occurring at the ends of long bones in skeletons free from general change.

Parathyroid Disturbances.—Quick and Hunsberger [10] reported a case of hyperparathyroidism in a man of 21 who became helplessly deformed in three years. The first symptoms were polydipsia, polyuria, a persistently milky urine and sharp myositic and arthritic pains. The roentgenograms showed decalcification of the bones and considerable calcification of the peripheral arteries. A persistent hypercalcemia was found. A parathyroid tumor was found and removed with considerable difficulty. General improvement followed the removal of the tumor. The authors advised the use of vitamin D or viosterol to minimize parathyroid tetany and to hasten the recalcification after the removal of a parathyroid tumor.

Parathyroid Extract.—In an editorial [11] in *The Journal of the American Medical Association* the influence of parathyroid extract on bone salts was discussed. A hypofunction of the parathyroid gland appeared to exert an inhibiting effect on the rate of healing of fractures while administration of the glandular hormone seemed to favor calcification and union of fractures. When parathyroid extract was injected, a marked increase in the blood calcium resulted. Experiments by Tsai and Hsu afforded evidence that the origin of the increased calcium concentration was from the bones. The difficulty of raising the blood calcium level by giving large doses of viosterol to parathyroidectomized animals and the failure to raise the concentration of calcium in the blood of animals deprived of vitamin D were additional suggestive observations that the calcium came from the bones through the stimulus of parathyroid extract. As studies of the calcium balance in lactation also showed, the bones were a readily available reservoir of mineral salts. Extraction and deposition of calcium in relation to the bones were

10. Quick, A. J., and Hunsberger, A., Jr.: Hyperparathyroidism: Clinical Picture in Far Advanced Stage, J. A. M. A. **96**:745 (March 7) 1931.

11. Influence of Parathyroid Extract on Bone Salts, Editorial, J. A. M. A. **96**: 443 (Feb. 7) 1931.

probably being carried on constantly in the body after the removal of a parathyroid tumor.

TUBERCULOSIS

Future Research.—Long,[12] in discussing the recent advances in research on tuberculosis, mentioned the finding of nonacid-fast forms of the tubercle bacillus which were highly pathogenic, but which were rarely found in cold abscesses. Pleomorphic forms and even filtrable viruses produced the pathologic picture of tuberculosis in animals. Another advance was the division of tubercle bacilli into rough and smooth forms, the smooth form being of high pathogenicity and growing best in alkaline mediums and the rough form of low virulence and growing best in acid mediums. The rapid changes in form and virulence in the same strain of the bacillus tuberculosis, the author considered a potent argument against vaccination for tuberculosis. Opinions in tuberculosis of any type should be based on disturbed function rather than on altered structure and should never be based on roentgenograms alone. In the treatment for the disease no specific drug had been found of definite value. The increased application of heliotherapy was the best measure in nonpulmonary tuberculosis. A high monocyte count was of unfavorable significance. The future work should be on prevention of transmission rather than on vaccination which was still *sub judice*.

Treatment.—Gaugele [13] advocated the use of careful, active, assisted motion in tuberculous joints after the acute stage was past in preference to the older method of immobilization for a long period of time with the hope that bony ankylosis would result. The patients treated this way were either kept in traction or used nonweight-bearing splints (Hessing type) for a long period. Early results were good, but no case is of long enough duration for final judgment to be passed.

SPINAL LESIONS AND BACK PAIN

Intervertebral Disk.—Schmorl [14] pointed out that calcification of the nucleus pulposus of the intervertebral disk was a rather rare occurrence. Very rarely the whole disk was calcified. The calcification of the nucleus was a sign of degeneration. Calcification and ossification were not the same. In infectious spondylitis the intervertebral disks were rarely affected.

Lyon [15] disagreed with the opinion of Schmorl that the intervertebral disks were but rarely affected in infectious spondylitis on the basis of the literature and x-ray pictures. In typhoid spondylitis the intervertebral disk was often calcified in the healing process.

12. Long, E. R.: Colorado Med. **28**:5, 1931.
13. Gaugele, C.: Chirurg. **2**:163, 1930.
14. Schmorl, G.: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:18, 1929.
15. Lyon, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:635, 1929.

Schmorl [16] described small enchondromas on the posterior aspect of the intervertebral disks. He believed that they originated through the tearing off of the edge of the intervertebral disk; the soft tissue of the nucleus pulposus was then forced out beneath the posterior longitudinal ligament and cartilage proliferation followed. Where the enchondroma was somewhat calcified, it could be demonstrated in the roentgenograms.

[ED. NOTE.—Schmorl's studies of spinal pathology have been far-reaching and his contributions on lesions of the nucleus pulposus deserve careful study.]

Low Back Pain.—Miltner and Lowendorf [17] reviewed the records of 2,050 cases of low back pain at the University of Iowa Hospital, and found the causative factors to be as follows: (1) osteo-arthritis, 1,350 cases; (2) sacro-iliac and sacrolumbar strain, 525 cases; (3) muscle strain, 100 cases; (4) lumbar myositis, 25 cases, and (5) rarer lesions, such as fractures of the transverse process, spondylolisthesis, etc., 50 cases.

They emphasized the importance of a careful history and an accurate physical examination, making use of the special tests in a differential diagnosis. The roentgenogram was relied on relatively little except as a means of ruling out gross deformity or disease. The chief means of treatment consisted of (1) rest in the acute cases followed by (2) physical therapy and exercises supplemented by support in the form of (3) brace or belt, (4) manipulation, and (5) operative treatment, which was resorted to only in the resistant cases.

Spondylolisthesis.—According to Meyerding,[18] prior to 1900 only 125 cases of spondylolisthesis had been recorded in the literature, and all but 6 of these had been reported by obstetricians or gynecologists. With the perfection of roentgen technic, however, the diagnosis became easy. From 1918 to 1930, 121 cases were observed at the Mayo Clinic. Sixty-two per cent were in males, and the average age was 37 years. Thirty-eight per cent ascribed the deformity to trauma. The symptoms were low backache, pain in the legs, and at times numbness and tingling. Rest usually gave relief, as did a plaster jacket or brace. Fusion of the lumbosacral spine, however, offered the most permanent form of relief.

Four cases of spondylolisthesis were reported by Kleinberg [19] in which the conditions seemed to be due to a congenital deformity of the posterior arch of the fifth lumbar vertebra. In two of these cases there was a cleft in the pedicles with a wide separation of the superior and

16. Schmorl, G.: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:629, 1929.
17. Miltner, L. J., and Lowendorf, C. S.: J. Bone & Joint Surg. **13**:16, 1931.
18. Meyerding, H. W.: J. Bone & Joint Surg. **13**:39, 1931.
19. Kleinberg, S.: Am. J. Surg. **10**:521, 1930.

inferior articular processes. In the other two the laminae were attenuated and abnormally long. In all of these cases trauma was an important factor in bringing on symptoms. The author believed that a fusion operation was imperative where there was a cleft in the pedicles. In the type with abnormally long laminae some external spinal support should first be tried for the relief from pain.

POLIOMYELITIS

Immunization.—A recent editorial [20] in *The Journal of the American Medical Association* gave a summary of the knowledge on immunology in poliomyelitis. Most investigators were convinced that poliomyelitis was caused by one of that still vague category of agents, the filtrable viruses. Flexner and Lewis and Levaditi and Landsteiner discovered in 1910 that the serum of patients convalescent from poliomyelitis was capable of neutralizing the filtrable virus. According to Park, the serum from slight abortive cases was on the average as potent as that from pronounced cases. The serum of many persons who have never had poliomyelitis contained antibodies, but these were not so potent as in the serum of convalescent cases. The antibodies remained for a long time in the blood of persons who were convalescent. Rhoads recently discovered that poliomyelitis virus could be inactivated by suspensions in aluminum hydroxide. This reaction was promoted by an acid medium and could be prevented by an alkaline environment. The striking feature, however, was the demonstration that the virus, when absorbed in aluminum hydroxide, was incapable of producing poliomyelitis but was still capable of inducing active immunity in monkeys (Macacus rhesus). In a small series of animals thus immunized symptoms of experimental poliomyelitis did not appear, and in only one was the degree of immunity, although adequate to protect against nasal injection, sufficient to protect against intracerebral injection of virus. Intracerebral inoculations of the aluminum suspension alone were without pathologic effect. The mere recital of these experiments offers a bright prospect of helpful possibilities in the attack on infantile paralysis. It has depended and will continue to depend on animal experimentation.

Stewart and Platou [21] stated that the use of convalescent serum was of definite value in the preparalytic stage of poliomyelitis. They advised the use of from 20 to 30 cc. intrathecally and 50 cc. intravenously. They advised a wider use of prophylactic doses of from 10 to 20 cc. of convalescent serum subcutaneously to exposed children during an epidemic.

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20. Immunization Studies in Poliomyelitis, Editorial, J. A. M. A. **96**:119 (Jan. 10) 1931.

21. Stewart, C. A., and Platou, E. S.: Minnesota Med. **14**:42, 1931.

Neustaedter [22] reviewed the work of Flexner in which immune bodies against poliomyelitis could not be obtained after the injection of filtrable virus into the horse. In 1916, the author injected into a horse trypsinized filtrates of cord and brain suspensions of children that died of poliomyelitis. The serum of this horse protected one monkey completely from an intracerebral inoculation of 0.5 cc. of a 5 per cent suspension of a very potent virus. Since that time three more horses have been inoculated with equally good results. It was found possible to concentrate this serum sufficiently to neutralize 100 parts of poliomyelitis virus in vitro. The author stated that the efficacy of this serum, and that of Pettit of Paris who followed his method, had been shown in over sixty frankly paralytic cases of poliomyelitis.

Diagnosis.—Allaria [23] gave a résumé of the present knowledge determining the diagnosis of acute anterior poliomyelitis, paying especial attention to the importance of abortive cases and of so-called carriers. He stressed the importance of quarantine and urged that it be carried out for a month, or better, for a month and a half. The author stated that the use of serum from patients who have recovered was of value if given early, as was probably also the serum from horses immunized by the method of Pettit.

[Ed. Note.—Evidence is steadily accumulating that tends to show the value of serums in the preparalytic stage of poliomyelitis. Unfortunately, it is in this stage that diagnosis is peculiarly difficult. The development of mass immunization or a rational form of temporary immunization during epidemics is suggested by these papers as a possible method of bringing the disease under control.]

PYOGENIC INFECTIONS

Osteomyelitis of the Spine.—Carson [24] recorded four cases of subacute osteomyelitis of the spine, three in adults and one in a child. All recovered. In three of the four the illness began with a boil on the skin. The genito-urinary tract was also involved in every case. Staphylococcus aureus was cultivated from all four patients. Three developed an abscess in connection with the spine. Attention was directed to the spine by severe nerve root pain.

Epiphysitis.—Miller [25] studied seventy-seven cases of acute transient epiphysitis of the hip. The average age of the patients was 7½ years.

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22. Neustaedter, M.: Antipoliomyelitis Horse Serum, J. A. M. A. **96**:933 (March 21) 1931.

23. Allaria, G. B.: Riforma med. **41**:1779 (Nov. 10) 1930.

24. Carson, H. W.: Brit. J. Surg. **18**:400, 1931.

25. Miller, O. L.: Acute Transient Epiphysitis of Hip Joint, J. A. M. A. **96**: 575 (Feb. 21) 1931.

The average duration of the symptoms before admission to the hospital was seven weeks. The average temperature on admission was slightly more than 100 F., and elevation of temperature was noticed for five weeks. The average leukocyte count on admission was 15,000 with 81 per cent polymorphonuclear cells. The average time of duration of symptoms, local or general, after admission to the hospital, was six weeks. Miller found this condition a common cause of hip complaint in children. It was usually provoked by mild trauma. It was suspected in a child who complained of pain about the hip if he had diseased tonsils or had recently had an acute infectious disease. Eighty per cent of the cases were associated with diseased tonsils. Carefully made roentgenograms suggested small abscess formation and absorption about the epiphyseal line. The treatment consisted of removal of infectious foci, rest from weight-bearing and traction of the involved limb. The duration of the disease was from a few weeks to a few months, and if prompt treatment was instituted, the children recovered without any permanent changes in the hip joint.

[ED. NOTE.—Some of the authors have observed a number of similar cases. In the majority of these, symptoms in the hip or knee followed a gastro-intestinal disturbance. With rest and regulation of the enteric tract, complete recovery ensued. Roentgenograms showed no changes. These cases were commonly diagnosed as toxic arthritis. If demonstrable changes can be observed at the epiphyseal line, the name acute, transient epiphysitis is a far more logical one for these cases.]

CHRONIC ARTHRITIS

Problem of Arthritis.—In an address before the New England Health Institute, Osgood [26] quoted statistics to indicate that arthritis was the most prevalent of the chronic ailments. He emphasized the fact that arthritis was a generalized disease with joint manifestations and that there were certain types of persons in whom there was a predisposition to the disease. He outlined the outstanding characteristics of the two great types, i. e., atrophic and hypertrophic arthritis. While local treatment of the joint was important, he stated that general treatment of the patient, especially early in the disease, was of the utmost importance.

In speaking of the developments in the problem of arthritis, Pemberton [27] said that in the opinion of most of the members of the American Committee for the Control of Rheumatism it was of the first importance to envisage arthritis as a whole instead of focusing on any

26. Osgood, R. B.: New England J. Med. **204**:55, 1931.

27. Pemberton, R.: Developments in Problems of Arthritis, J. A. M. A. **96**:33 (Jan. 3) 1931.

factor, be it mechanical, bacteriologic or nutritional, which may precipitate it. As in tuberculosis, the specific treatment was based on broad physiologic considerations, since the organism was of necessity practically ignored in a therapeutic sense, so in arthritis the treatment should be on broad physiologic grounds. No agency or organism was recognized by the committee as the single cause.

Treatment of Arthritis of the Spine.—Jepson and Brav [28] reported four cases of arthritis of the spine in which the patients were treated by manipulation to correct the forward flexion of the spine. Under ether anesthesia, the portion of the spine showing the greatest deformity was manipulated. Following manipulation a plaster cast as applied in hyperextension. This was followed by a brace. The authors felt that this method was of value where no bony ankylosis was shown by the roentgenogram.

[ED. NOTE.—While deformity in the spine may be corrected to a certain extent by this method, several of the authors have observed catastrophes following its use. Gradual hyperextension with sandbags or posterior shells will accomplish as much without injury, and in as short a time, considering the after treatment. In a number of cases ankylosis of the spine cannot be determined on roentgen evidence alone.]

NERVOUS DISORDERS

Tabetic Arthropathy.—In discussing the tabetic arthropathies, Steindler [29] stated that while it must be expected that the neurogenic background predisposed the joint to arthropathic disintegration, it seemed certain that mechanical and traumatic events were the determining factors that sooner or later led to the breakdown of the articulation. Protection against these influences by early and adequate splinting, preservation of protecting musculature by physical therapy and, above all, early stabilization and alinement by conservative or operative means furnished the best prospects of extending the usefulness of these joints for many years. Steindler advised detection of the arthropathic joint by roentgen examination in the preataxic stage, and then immediate and adequate protection of the joint to prevent the action of detrimental external influences.

From his own observations, Iselin [30] came to the conclusion that in cases of so-called tabetic arthropathia the tabes was not the only underlying cause, but that in many cases the disease was caused by a combination of syphilis, other infections, nutritive disturbances and nervous

28. Jepson, P. N., and Brav, E. A.: Am. J. Surg. **10**:285, 1930.

29. Steindler, A.: The Tabetic Arthropathies, J. A. M. A. **96**:250 (Jan. 24) 1931.

30. Iselin, H.: Deutsche Ztschr. f. Chir. **227**:414, 1930.

damages of tabetic origin. Of these syphilis seemed to be most important. The syphilis could be reactivated by traumatism or without any special cause within the arthropathic joint.

[ED. NOTE.—We think that Steindler has voiced the consensus of orthopedic opinion in regard to the etiology of tabetic arthropathy.]

Ramisection in Spastic Paralysis.—Carrell [31] studied the end-results in eighty-three sympathetic ramisections; twenty-three cervical and sixty lumbar. There were no differences in the character of the reflexes before or after the operations. The record of footprints did not give any particular information. No change was observed in fixed contractions or in those contractions that developed on attempting motion or excitation, as scissor gait, equinus or valgus of the foot. Relief of contractions by other operations had been necessary, but it was noted that a paraplegia of equal spasticity had better function in the leg with lumbar ramisection and section of the obturator than with obturator section alone. Carrell concluded that the severity of physical disability and mental development were the two important factors influencing the progress after such operation. Where it was necessary to choose between ramisection and Stoffel's operation with foot stabilization, the latter procedure seemed to meet more indications, and they gave a higher percentage of improvement in a large series of cases.

Compression of the Cord by Bony Plaques.—Four cases of compression of the spinal cord by bony plaques in the meninges were reported by Punsepp.[32] Osseous deposits in the arachnoid, while frequently observed, gave no symptoms. Trauma probably played a rôle in these cases. These bony plaques were characterized by an abundant formation of connective tissue in which the osseous deposits occurred. In these four cases laminectomy was performed after neurologic symptoms, and block with iodized poppy seed oil 40 per cent showed the area involved. One patient died of cardiac failure. There was complete recovery in the other three.

NEOPLASMS

Osteitis Fibrosa Localisata.—Ferbert [33] studied the localized form of osteitis fibrosa in adults. He found this form most frequent in young adults in the form of a solitary cyst of the bone. Adults in middle or old age were affected much less frequently. In these cases the formation of an actual cyst was not as typical as the formation of fibrous marrow, osteoid and bony new growth. Prognosis was comparatively favorable. The disease might last for many years without much change

31. Carrell, W. B.: Sympathetic Ramisection in Spastic Paralysis, J. A. M. A. **96**:849 (March 14) 1931.
32. Punsepp, L.: J. Nerv. & Ment. Dis. **73**:1, 1931.
33. Ferbert, H.: Ztschr. f. orthop. Chir. **53**:285, 1930.

or disturbance of function. Consequently, the therapy should usually be conservative. Operative treatment was indicated to correct deformity or to improve the appearance by removal of hypertrophic bone. Differentiation from Paget's disease consisted in that the latter had a marked progressive tendency, whereas osteitis fibrosa, especially in the localized form, usually came to a standstill, and did not spread to other parts of the skeleton.

[ED. NOTE.—Pathologic fracture is a frequent complication of localized osteitis fibrosa. We have observed cysts that have persisted in spite of two or three fractures, and we think that operative treatment is indicated under such conditions.]

MISCELLANEOUS

Malacia of the Semilunar and Scaphoid Bones of the Wrist.—Santozki and Kopelmann [34] made a study of nineteen cases of malacia of the semilunar and scaphoid bones of the wrist. They considered the process to be an aseptic necrosis of the bones, and that the cause was an obliteration of the nutritive vessels brought about by chronic occupational traumatism. Individual predisposition played a part. In the opinion of the authors early excision was the best treatment.

Blaine [35] considered that the essential change was a softening of the bones with necrosis and deformity. He thought that a twist of or a blow on the wrist was of common occurrence, and merely resulted in the roentgen disclosure of a preexisting pathologic condition in the semilunar or scaphoid bones. Discussing the etiology, the author mentioned the various theories such as embolic obstruction to the arterial supply and the relatively poor normal blood supply to these bones, and said that since the factors of etiology, symptomatology and pathology were more or less identical with similar lesions that have been found to involve various other osseous structures of the body, it seemed logical to consider the process essentially the same, namely, osteomalacia. He felt that surgical removal of the diseased bone did not materially reduce the disability.

On the other hand, Schnek,[36] from his studies of the so-called posttraumatic cysts of the scaphoid bone (another name for the same process in the opinion of the editors), came to the conclusion that these cysts were the sequelae of unrecognized and improperly treated fractures of the scaphoid bone. His own experience convinced him that there was a great difference between this condition and actual pseudarthrosis of the

34. Santozki, M., and Kopelmann, S.: Fortschr. a. d. Geb. d. Röntgenstrahlen **39**:1060, 1929.

35. Blaine, E. S.: Lunate Osteomalacia, J. A. M. A. **96**:492 (Feb. 14) 1931.

36. Schnek, F.: Fortschr. a. d. Geb. d. Röntgenstrahlen **39**:1016, 1929.

scaphoid in that the cystic condition and likewise the fresh fracture could always be cured by complete and prolonged immobilization, while the pseudarthrosis did not respond to this method of treatment.

[ED. NOTE.—We believe that the opinions of Santozki and Kopelmann and of Blaine in respect to the etiology of malacia of the scaphoid and semilunar bones or Kienboch's disease will obtain greater acceptance than Schnek's. We believe, however, that trauma, either occupational or single, is a factor. We agree with Schnek that prolonged fixation of the wrist will often bring about a cure, and that excision is rarely necessary.]

Semilunar Cartilages of the Knee.—Israelski [37] reported three instances of calcification of the menisci revealed by roentgen examination. All occurred in patients past middle life, and did not follow trauma. The author thought that a metabolic factor might be the cause since one patient had gout and another diabetes. In one there was also calcification of one of the intervertebral disks.

Mandl [38] observed regeneration of previously excised semilunar cartilages in two patients; one was found accidentally at autopsy, and the other at a later operation on the same knee joint. He was surprised to find an almost complete regeneration of the cartilage in both cases.

Changes in the Hip Joint in Hemophilia.—Loehr [39] examined and studied patients whose hip joints had been affected by hemophilia. The bleeding might be intra-articular or extra-articular, or even within the bony tissue. It might occur once or repeatedly, usually in early age, but sometimes even after the age of puberty. The hip joint was relatively rarely affected compared with the elbow and knee joints. Both of Loehr's patients were of preadolescent age, and showed typical signs of osteochondritis deformans juvenalis. The study of the cases reported in the literature showed that all patients who had hemophilia affecting the hip joint who had been affected before puberty showed the same condition, while patients who had been affected at a later age showed changes of a different nature, such as coxa valga, cystlike development in the neck of the femur, in the head and in the acetabulum with more or less evidence of arthritis deformans.

BONE, JOINT AND TENDON SURGERY

Physiologic Reconstruction of the Thumb after Total Loss.—The operative procedure for the reconstruction of a functioning thumb from a second metacarpal and the proximal half of the first phalanx attached

37. Israelski, M.: Am. J. Roentgenol. **25**:85, 1931.
38. Mandl, F.: Zentralbl. f. Chir. **52**:1929, 1930.
39. Loehr, D.: Ztschr. f. Chir. **228**:234, 1930.

to it was reported by Bunnell.[40] The transplantation was done so as to preserve nerve, blood and lymph supply. The second metacarpal was transplanted to the trapezium, and the lower 3 inches (7.6 cm.) of the tendon of the flexor carpi radialis was passed through drill holes in the metacarpal and trapezium to insure a stable joint. The cut tendon was then attached to the flexor carpi radialis brevis. The three extensor tendons of the thumb were attached to the second metacarpal at their usual locations. The flexor tendons of the thumb were attached to the flexor tendons of the transplanted index finger. The thenar muscles were reattached to the transplanted second metacarpal. An excellent functional result was obtained. The author gave as requisites of a transplanted thumb: sensation, motion particularly in opposition to fingers, strength and durability.

Complete Rupture of the Supraspinatus Tendon.—Wilson [41] stated that an experience with ten patients with complete rupture of the supraspinatus tendon in a period of eighteen months had impressed him with the frequent occurrence of this injury. The pathologic observations at operations indicated gradual weakening of the tendon previous to rupture. The lesion should be suspected in any patient who gave a history of shoulder disability of sudden onset and particularly when a painful snap has occurred during a movement of abduction or when there had been a fall on the shoulder with or without dislocation. The characteristic sign of rupture was inability to abduct actively while this movement might be executed passively. This sign might be masked by muscle spasm or adhesions. Repair of the tendon was rendered difficult by the extent of the gap in the capsule, and it was important not only to suture the tendon to the greater tuberosity, but to provide means whereby it might develop a real bony attachment throughout its breadth. The results of operation showed that the disability could be removed and emphasized the importance of recognizing this lesion which was frequently overlooked.

Operative Treatment of Scoliosis.—In three patients with severe scoliosis with marked listing to the side, Schede [42] used a massive graft from the tibia to hold the trunk upright. The graft was inserted between the transverse process of the first lumbar vertebra and the rim of the pelvis. The end-results were as follows: In one patient the graft was absorbed, but in the other two the graft hypertrophied to about three times its original width and gave excellent support to the trunk. While in all cases the graft became firmly united to the trans-

40. Bunnell, S.: Surg., Gynec. & Obst. **52**:245, 1931.

41. Wilson, P. D.: Complete Rupture of the Supraspinatus Tendon, J. A. M. A. **96**:433 (Feb. 7) 1931.

42. Schede, F.: Zentralbl. f. Chir. **57**:2658, 1930.

verse process of the first lumbar vertebra, it developed an articular union to the rim of the pelvis in the form of a saddle joint.

Preoperative Determination of the Best Functional Position for Ankylosis of the Hip.—Adams,[43] from a study of ankylosed hips, concluded that a definite position could be determined in each case which would give the best functional result. When ankylosis of the hip was produced by operation, the hip could be fixed in this ideal position. The best functional position was determined by studying Kingsley's table for normal flexion and Lovett's table for abduction and apparent shortening.

[ED. NOTE.—There has been a wide variance of opinion as to the best functional position for ankylosis of the hip, and the tendency has been to assume that the position should be the same for all persons, an attitude that is manifestly wrong because it does not take into consideration such factors as shortening, etc. Adams has done a careful piece of work, and his article should be studied, and the rules laid down for determining the optimum position of the hip followed.]

Correction of Deformed Feet.—Basing his practice on careful study of bone regeneration and on animal experiments, Matti[44] developed a technic for correction of foot deformities and for foot stabilization in which he saved the bone obtained from the wedge-shaped excisions about the joints, cut it up into many small fragments, and transplanted the bone chips in between the denuded bone surfaces in such a position as to help maintain the corrected position. For example, in the correction of club feet he put them in on the medial side. He pointed out that bone survived the earlier and more completely it got in touch with the circulation of blood and lymph. Hence a large piece of compact bone was at a greater disadvantage than a small piece of spongy bone. His experiments on animals showed that chips of cancellous bone remained living for a long time, and served well in filling bony defects. He used the same principle in the operative correction of deformities of long bones and in the treatment for pseudarthrosis.

Rey[45] recommended the resection of the medial plantar nerve as a reliable and simple method for the cure of claw foot. The method had the advantage of attacking those muscles that were concerned with the production of the deformity and by the action of which recurrence was brought about. In patients with severe deformities, the lateral nerve

43. Adams, A. O.: Surg., Gynec. & Obst. **52**:261, 1931.
44. Matti: Zentralbl. f. Chir. **57**:796, 1930.
45. Rey, J.: Ztschr. f. orthop. Chir. **53**:322, 1930.

might be resected also and in addition the long peroneal tendon was transplanted into the short peroneal tendon, and the division of the plantar fascia was performed. In cases in which the tarsus showed severe deformation, bony resections should be done beforehand, later followed by the resection of the nerves. The following muscles were of the greatest importance in the development and in the later recurrence of pes cavus: the short flexor muscles of the toes, the long peroneal muscle, and often the abductor hallucis. Of lesser importance were the long flexor and the posterior tibial muscles, and still less the triceps surae.

Whitman [46] described an operation for the correction of equino valgus deformity resulting from paralysis of the tibialis anticus or posticus muscles, or both. It consisted in subastragalar and astragaloscaphoid arthrodesis through a mesial incision. Then the anterior tibial tendon was divided at its junction with the muscular fibers, dissected free from its sheath and passed under and then over the tendons of the extensor communis digitorum and extensor hallucis longus, and finally buried subperiosteally in the tibia.

The operation had been done eight times in seven patients. The author stated that all patients were satisfied with their results.

[Ed. Note.—It is of interest to note that here are described three methods involving the use of three different principles for the operative correction of foot deformities: wedge-shaped excision and arthrodesis of joints, resection of the nerves supplying overacting muscles and the use of tendon loops to restrain and improve the lines of muscle pull. With the first principle, all of us are in accord. Remodeling of the bony architecture with arthrodesis of the unstable joints is the foundation stone on which everything else is built. Readjustment of muscle pulls, we believe, can be more satisfactorily brought about by tendon transplantation than by the use of a tendon loop. With the resection of the nerves to the overacting muscles in pes cavus we have had no experience, but the method may well have a use.]

FRACTURES

Pseudarthrosis.—Bauer [47] recommended Kirschner's splintering method in the treatment for pseudarthrosis. He had had good results in the majority of the patients he had treated, although all the cases were of long standing and some had been subjected to previous operation without success. He moved and shifted the splinters about as the case demanded in order to peg the fragments, and when the nutritive conditions were particularly bad, he added autoplastic fragments of bone from other parts of the body.

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46. Whitman, A.: J. Bone & Joint Surg. **13**:122, 1931.
47. Bauer, K. H.: Chirurg. **19**:871, 1929.

In a discussion of the causes of pseudarthrosis, Koenig [48] stated that he had frequently found soft tissue interposed between the fragments, and he thought that this was one of the chief causes of delayed union. On the other hand, union might take place in spite of interposition of soft tissues.

Bier [49] maintained the view that mechanical factors played a subordinate part in producing delayed union. More important were faulty nutrition and chemical disturbances, especially the lack of hormones due to altered innervation. In such cases he relied on general rather than local treatment. In obstinate cases he employed Kirschner's bone splintering method.

Boehler [50] recommended drilling many holes into the bone near the ends of the fragments, or the old method of refracturing recently again recommended by Goetze.

Skeletal Traction.—Fitzgerald,[51] describing the advantages and disadvantages of various methods of skeletal traction, pointed out that the use of the Kirschner wire was probably the most satisfactory in that with it there was less trauma and consequently less danger of infection than with ice tongs and Steinman's pin. Also the wire was more efficient. The technic of the use of Kirschner's wire was described.

Speed [52] advocated the use of steel pins of small caliber that could be driven through the bone and whose ends protruding through the skin could be covered with sterile dressings and embedded in plaster of paris casings, and thus serve to maintain position in fractures of the leg. The method necessitated previous complete reduction of the fracture, but the fixation was absolute and safe when the plaster had hardened.

[ED. NOTE.—We concur with Fitzgerald in respect to the advantages of Kirschner's wire over the ordinary skeletal pins and ice tongs. The patient is usually more comfortable, there is less risk of infection, and the wounds heal more promptly. We believe there are advantages in embedding pins in plaster casings when the fracture can be completely reduced. This method is particularly valuable in the treatment for fractures of the bones of the leg in that it provides complete immobilization, and this ought to be important in reducing the incidence of delayed union and nonunion.]

Fractures of the Head and Neck of the Radius.—From the standpoint of treatment, Key [53] divided fractures of the upper end of the radius

48. Koenig, F.: Deutsche med. Wchnschr. **56**:939, 1930.
49. Bier: Deutsche med. Wchnschr. **56**:939, 1930.
50. Boehler, F.: Deutsche med. Wchnschr. **56**:939, 1930.
51. Fitzgerald, E. R.: Canad. M. A. J. **24**:83, 1931.
52. Speed, K.: Surg., Gynec. & Obst. **51**:854, 1930.
53. Key, J. A.: Treatment of Fracture of the Head and Neck of the Radius, J. A. M. A. **96**:101 (Jan. 10) 1931.

into three groups: The first group consisted of those that ought to be treated conservatively, namely, fissure fractures of the head, chip or chisel fractures of the head in which the detached fragment comprised less than one third of the circumference of the head, and was not displaced or did not lie against the ulna, and fractures of the neck in which there was practically no displacement of the upper fragment. The second group consisted of fractures that ought to be treated by operation, namely, comminuted fractures of the head, chip or chisel fractures of the head in which a fragment larger than a third of the head was detached or displaced, or in which a small fragment was separated in close relation to the articulation with the ulna, and fractures of the neck in which the head was displaced downward or so tilted that its rounded border could no longer rotate in the sigmoid of the ulna and in which the displacement could not be reduced by manipulation. In the third group were those cases in which treatment should be conservative at first, and operation done later if necessary. This group included all doubtful cases of group 1, that is, cases with chip fractures of the neck with slight displacement, chip fractures with considerable displacement of the detached fragment which might be loose in the joint and fractures of the neck with complete and extensive displacement of the head which usually lay embedded in the tissues beneath the flexor muscles of the forearm and could no longer block motion at the elbow.

Fracture of the Capitellum.—Boehler [54] pointed out the importance of distinguishing between the isolated fracture of the capitellum with forward displacement and rotation and the shearing off of the articular cartilage of the capitellum with posterior displacement. The former lesion was encountered only in persons with a hyperextensible elbow; the latter only in persons with a valgus elbow. These lesions could therefore be produced only when there were proper preexisting constitutional conditions. They should be differentiated from other fractures of the lower end of the humerus.

Traumatic Myelitis Resulting from Fractures of the Spine.—Gurdjian [55] studied seventy-two cases of fractured spine with transverse myelitis. The cord injury was produced by either direct or indirect violence, i. e., either due directly to pressure from the bony vertebral column or simply by concussion. Central softening of the cord was a frequent finding in fractured spines, and might extend up the cord for some distance from the site of injury. The fractures were either compression or chip fractures of the bodies of the vertebrae. Of thirty-two compression fractures, nineteen were lumbar, seven were dorsal and six were in the cervical spine. Careful technic should be exercised in obtain-

54. Boehler, L.: Arch. f. Orthop. **28**:734, 1930.

55. Gurdjian, E. S.: Am. J. Roentgenol. **25**:65, 1931.

ing good anteroposterior and lateral roentgenograms, particularly of the cervicodorsal junction, a not infrequent site of fracture.

Fractures of the Pelvis.—Nineteen cases of fracture of the pelvis were reviewed by Parker.[56] They constituted 3 per cent of all fractures observed. The author found that the gravity of the injury depended on the amount of damage to the structures within the pelvis. There were two deaths from shock. The injury was produced in most cases by a rolling or squeezing force or by an automobile crush. A few cases were caused by a severe fall. The common associated injuries were ruptured bladder, ruptured urethra, ruptured kidney and fractures other than those of the pelvis. After examination for complications the patients were placed flat in bed and the position maintained with sandbags to the legs and pelvis. In a few cases traction and abduction were used where there was marked upward displacement of the ilium. A pelvic belt was used when there was separation of the sacro-iliac joint or symphysis pubis. The average stay in the hospital was thirty-nine days. Good functional results were obtained in thirteen cases.

Fracture of the Bones of the Leg.—Kennedy [57] presented a study of 114 patients with fractures of the bones of the leg, who had been treated at the Beekman Street Hospital between 1924 and 1929. Many of them were severe compound fractures. The favorite form of treatment in most cases was skeletal traction by means of Steinman's pin through the os calcis with the leg suspended in a Thomas splint. Fixation in plaster was employed primarily in 70 patients, but in 14 proved unsatisfactory and had to be abandoned in favor of skeletal traction. Operation was avoided as much as possible, the danger of tetanus being considered real because of the frequent contamination of the skin with horse manure. The Massachusetts General Hospital system of rating the end-results at the end of one year on the basis of the anatomic, functional and economic results was employed.

[Ed. Note.—The article represents a thorough study and deserves to be read. The results obtained are a recommendation for the methods of treatment used.]

DISLOCATIONS

Disruption of the Pelvis with Luxation of the Innominate Bone.—Eight cases of luxation of the innominate bone were reported by Peabody.[58] The displacement was associated in each case with a fracture of the pelvic ring or separation of the symphysis pubis. One of these patients

56. Parker, O. W.: Minnesota Med. **14**:29, 1931.

57. Kennedy, R. H.: Ann. Surg. **93**:563, 1931.

58. Peabody, C. E.: Disruption of Pelvis with Luxation of Innominate Bone, Arch. Surg. **21**:971 (Dec.) 1930.

died immediately, one could not be traced, and the others completely recovered. The injury was produced either by a fall, or by a crushing or twisting force acting on the pelvis. Visceral complications were rarely seen. Severe sciatica was observed only in patients with an accompanying fracture of the fifth lumbar vertebra. Treatment was traction on the leg of the involved side under anesthesia followed by manipulation with the aid of the fluoroscope. After reduction a webbing belt was tightly applied around the pelvis and the patient placed on a Bradford frame with traction on the leg of the injured side. In two cases rotary redisplacement required wiring of the symphysis pubis. Ankylosis of the involved sacro-iliac joint occurred in all of the cases followed.

Chronic Subluxation of the Distal Radio-Ulnar Joint.—Berry [59] reported the case of a youth, aged 20, who after a Colles' fracture was unable to resume his work as a carpenter, owing to undue anteroposterior mobility of the lower end of the ulna on the radius. Quite slight pressure on the palm of the hand would cause the head of the ulna to project backward. Berry, therefore, fused the distal radio-ulnar joint by removing the opposing cartilaginous surfaces and driving a bone peg through the ulna into the radius, and at the same time resected 1 inch (2.5 cm.) of the ulna in its lower fourth. Following the operation, the patient was able to resume his work and even to mix concrete with a shovel. Supination and pronation were perfect.

[ED. NOTE.—Berry's method of dealing with chronic subluxation of the distal radio-ulnar joint deserves consideration. It is not as simple as fixation of the head of the ulna to the radius by fascial suture, but it may be more positive in its results. The result achieved in this single case merits further trial of the method.]

RESEARCH

The Rôle of the Macrophage in Absorption from Synovial Cavities.—Rynearson [60] studied the absorption of various dye substances from the synovial cavities of dogs. He observed that the rôles played by the secretory cells and by the macrophages were different. The former were penetrated only by colloid substances, whereas the macrophages absorbed the particulate matter. While the colloid substances and fluids were carried away through the blood and lymph, the dye-stained macrophages were found in the case of the knee joint chiefly in the inguinal and lumbar lymph nodes and spleen. These observations suggested to the author that in arthritis the toxic substances might be absorbed by the secretory cells and that they were therefore carried to various parts of

59. Berry, J. A.: Brit. J. Surg. **18**:526, 1931.

60. Rynearson, E. H.: J. Bone & Joint Surg. **13**:127, 1931.

the body, whereas bacteria were transported only by the macrophages and carried to the lymph nodes.

[ED. NOTE.—Investigators in general have not been able to distinguish a true secretory type of cell in the synovial membrane and hence there may be some disagreement with this part of the author's conclusions.]

Influence of Alterations in Circulation on Repair of Bone.—Pearse and Morton,[61] in previously reported experiments, demonstrated that venous stasis accelerated bone repair. They carried their experiments further and found that in dogs obstruction of the lesser saphenous vein did not accelerate healing of the fractured fibula, probably because of the extensive anastomosis between this vein and the great saphenous vein. Obliteration of the femoral artery was found to delay healing, whereas lumbar sympathectomy had little effect on osteogenesis.

Fate of Transplanted Cortical Bone.—Davison and Kraff[62] attempted to determine the viability of autoplastic cortical bone grafted into cortical bone. Two dogs from the same litter were used for each experiment. One dog was fed sodium alizarin sulphonate which colored all new formed bone red from weaning until the dog was killed. A cortical graft from the temporal bone was transplanted from the dog given sodium alizarin sulphonate to the other dog and vice versa. The authors found that cortical bone transplanted aseptically and with perfect mechanical adaptation and fixation healed by primary intention and remained alive.

Regeneration of Hyaline Cartilage.—From a series of experiments on dogs, Shands[63] concluded that regeneration of hyaline cartilage might occur after injury. No regeneration was noted in less than four weeks. The various stages of repair were as follows: fibrin, granulation tissue, connective tissue, cartilage cells in connective tissue, fibrocartilage and new hyaline cartilage. No difference was found in the regenerative power of the cartilage in different areas of the joint. No definite evidence of a perichondrium was found. Direct trauma to the hyaline cartilage occasionally caused a proliferation of nests of new cartilage cells.

Myostatic Contracture Following Tenotomy.—Davenport and Ranson[64] studied the changes in the gastrocnemius muscle after tenotomy of

61. Pearse, H. E., and Morton, J. J.: J. Bone & Joint Surg. **13**:68, 1931.

62. Davison, C., and Kraff, A.: Fate of Cortical Bone Graft, Arch. Surg. **22**: 94 (Jan.) 1931.

63. Shands, A. R.: Regeneration of Hyaline Cartilage in Joints: Experimental Study, Arch. Surg. **22**:137 (Jan.) 1931.

64. Davenport, H. K., and Ranson, S. W.: Contracture Resulting from Tenotomy, Arch. Surg. **21**:995 (Dec.) 1930.

the tendo achillis in cats and rats. They pointed out that other observers had demonstrated that if the bony attachments of a skeletal muscle were left immobilized for several days so as to prevent the changes in length that normally resulted from spontaneous and reflex movement there occurred a fixation of the muscle at the length thus imposed on it. If taken early, this contracture could be overcome by active or passive movement, but if left untreated for some time the damage might become irreparable. This process called myostatic contracture by Davenport and Ranson was dependent on intact innervation. After it had developed, however, it persisted even after section of the motor nerve. According to the authors, it was an abnormal manifestation of tonic contraction. A muscle affected by this condition could not extend normally or contract normally.

Studying the myostatic contraction produced by tenotomy of the tendo achillis, the writers found an increase in the diameter of the muscle fibers, a more pronounced longitudinal fibrillation, blurred cross-striations, a dissociation of the membranes holding the myofibrils in alinement, a wavy contour in some of the fibers, light and dark irregularly outlined bands and an increase in the nuclei of the wandering cell type. There was no evidence of increase of the connective tissue elements. A 20 per cent loss in weight was found in the gastrocnemius muscle.

CORRECTION

In the article by Drs. Karl H. Martzloff and George E. Burget, entitled, "The Closed Intestinal Loop: III. Aseptic End-to-End Intestinal Anastomosis and a Method for Making a Closed Intestinal Loop Suitable for Physiologic Studies," in the July issue (**23**:26, 1931), an error occurred in the references at the bottom of page 29; reference 3 has been repeated and the first line of reference 5, omitted. These two references should read:

3. Rostowzew, M. I.: Aseptische Darmnaht, Arch. f. klin. Chir. **82**:462, 1907.

5. Rankin, F. W.: An Aseptic Method of Intestinal Anastomosis, Surg., Gynec. & Obst. **47**:78, 1928.

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